Synthesis of Multifunctional Organoboron Compounds by Copper-Catalyzed Enantioselective Reactions:

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SYNTHESIS OF MULTIFUNCTIONAL ORGANOBORON COMPOUNDS BY COPPER-CATALYZED ENANTIOSELECTIVE REACTIONS

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SYNTHESIS OF MULTIFUNCTIONAL ORGANOBORON COMPOUNDS BY COPPER-CATALYZED ENANTIOSELECTIVE REACTIONS

Zeyu Huang

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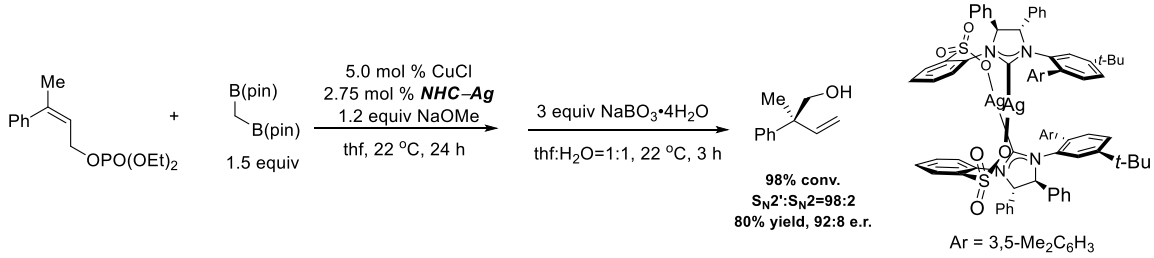
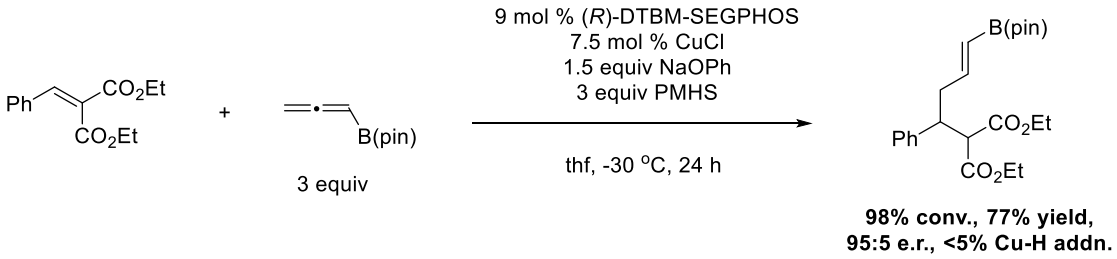
Abstract

Chapter 1. We have developed a catalytic method for enantio- and S_N2'-selective allylic substitution of commercially available diborylmethane to trisubstituted allylic phosphates (pin = pinacolato). The transformations are catalyzed by NHC–Cu complexes (NHC = N-heterocyclic carbene). Products bearing quaternary stereogenic carbon centers are obtained in up to 86% yield (after oxidation), >98:2 S_N2'/S_N2 selectivity and 95:5 enantiomeric ratio (e.r.).



Chapter 2. We have developed a facile multicomponent catalytic process that begins with a chemo- and site-selective copper–hydride addition to allenyl-B(pin) followed by enantioselective conjugate addition of the resulting allylcopper intermediate to α,β-

unsaturated malonate, generating products that contain a stereogenic center and an easily functionalizable alkenyl-B(pin) group in up to 84% yield, >98:2 *E*/*Z* selectivity and 96:4 enantiomeric ratio. The transformations are catalyzed by chiral Cu complexes derived from commercially available bisphosphines and CuCl.



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CHAPTER 1

SYNTHESIS OF ALKYL-B(PIN) WITH AN ALL-CARBON QUATERNARY STEREOGENIC CENTER BY CATALYTIC ENANTIOSELECTIVE ALLYLIC SUBSTITUTION WITH A DIBORYLMETHANE REAGENT

1.1 INTRODUCTION

One of the significant challenges in chemical synthesis is the development of efficient catalytic enantioselective reactions that furnish all-carbon quaternary stereogenic centers.[1] A general strategy for promoting such processes is the addition of carbon-based nucleophiles to electrophilic carbon sites. Copper-catalyzed enantioselective allylic substitution (EAS) is one of the most powerful carbon-carbon bond-forming reactions for the construction of stereogenic centers at the allylic position.[2] Significant progress has

(1) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2006. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci.* U.S.A. **2004**, *101*, 5363. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.

(2) For representative reviews, see: (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796-2823. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev*. **2008**, *108*, 2824–2852.

been made in the enantioselective allylic substitution with organometallic reagents (for example, Mg-, Zn-, and Al-based nucleophiles).[2]

More recently, methodologies utilizing organoboron reagents, which are more functional group tolerant and widely available, such as diborylmethane, have been reported.[3] We design the Cu-catalyzed enantioselective allylic substitution with di-B(pin)-methane to furnish compounds with all-carbon quaternary stereogenic centers as well as boronic ester and terminal olefin that can be easily transformed to other functional groups. We then applied this method to the synthesis of a bioactive molecule to highlight its utility.

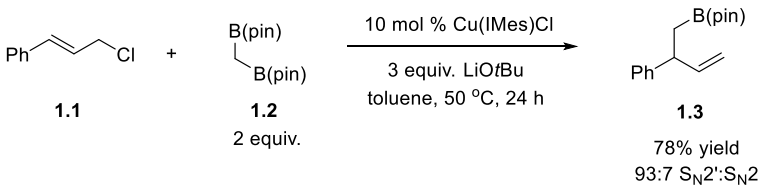
1.2 BACKGROUND

Diborylmethane reagent **1.2** was first synthesized by Matteson and co-workers in 1982.[4] Dichloromethane and lithium react with trimethylborate to generate the tetramethoxy diborylmethane. Then diborylmethane reagent **1.2** was formed by the addition of pinacol to tetramethoxy diborylmethane.

More recently, there has been reports on allylic substitutions with diborylmethane **1.2**. Cho and co-workers reported an NHC–Cu-catalyzed allylic substitution with diborylalkyl reagents (scheme 1.1).[3a] Alkyl-B(pin) containing products are obtained in up to 86% yield and >99:1 S_N2':S_N2 selectivity.

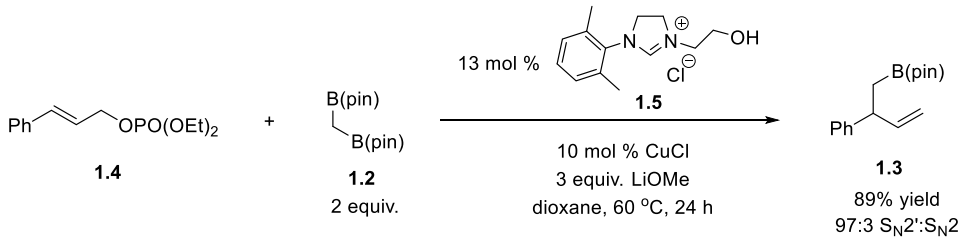
(3) For examples of allylic substitution with di-B(pin)-methane, see: (a) Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498–1501. (b) Zhang, Z.; Zhang, B.; Lu, X.; Liu, J.; Lu, X.; Xiao, B.; Fu, Y. *Org. Lett*. **2016**, *18*, 952-955. (c) Shi, Y.; Hoveyda A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455-3458. (d) Zhan, M.; Li, R. Z.; Mou, Z. D.; Cao, C. G.; Liu, J.; Chen, Y.; Niu, D. *ACS Catal*. **2016**, *6*, 3381-3386.
(4) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20–28.

Scheme 1.1 Cu-Catalyzed Allylic Substitution With Diborylalkyl Reagents



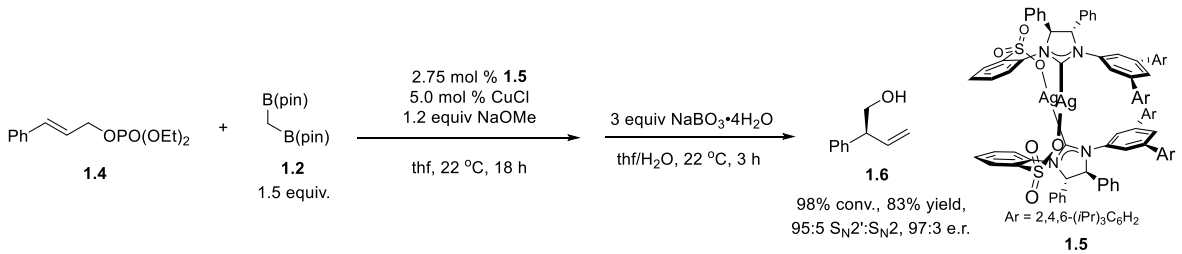
Fu and co-workers also reported a similar transformation (scheme 1.2).[3b] Products are obtained in up to 88% yield and 98:2 S_N2':S_N2 selectivity. Products containing quaternary carbon centers are also generated with high effiency.

Scheme 1.2 Cu-Catalyzed Allylic Substitution With Diboron Reagents



Hoveyda and co-workers reported the first enantioselective allylic substitution with diborylmethane **1.2** (scheme 1.3).[3c] A wide range of aryl- and alkyl-substituted allylic phosphates can be transformed to products in up to 95% yield (after oxidation), 99:1 e.r. and 98:2 S_N2':S_N2 selectivity. The author also highlighted the method with the formal synthesis of rhopaloic acid A.

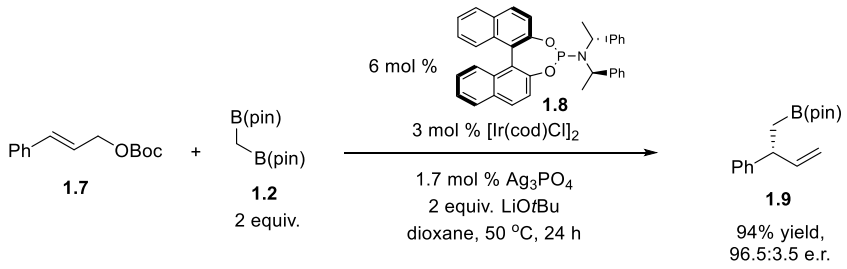
Scheme 1.3 Cu-Catalyzed Enantioselective Allylic Substitution With Diboron Reagents



Niu and co-workers also reported an Ir-catalyzed enantioselective allylic substitution with di-B(pin)-methane (scheme 1.4).[3d] Products are obtained from aryl allylic carbonates

in high effiency and enantiomeric ratio (up to 99% yield and 99:1 e.r.). The alkyl case reported is less efficient (one example with 24% NMR yield and N.D. e.r.).

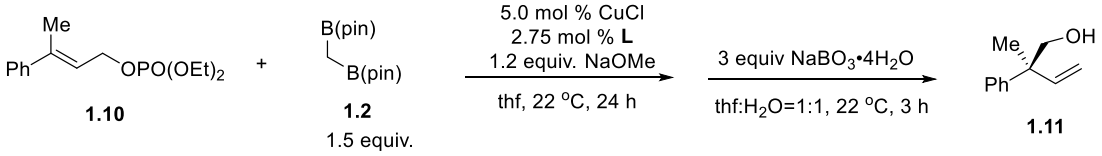
Scheme 1.4 Ir-Catalyzed Enantioselective Allylic Substitution With Diboron Reagents

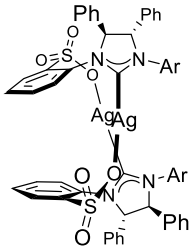


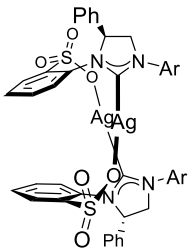
1.3 IDENTIFICATION OF THE OPTIMAL CATALYST FOR CATALYTIC ENANTIOSELECTIVE ALLYLIC SUBSTITUTION WITH A DIBORYLMETHANE REAGENT

We started our investigation from ligand screening for the methyleneboryl addition to *E*-allylic phosphate **1.10**. A variety of ligands, including different types of NHC-Ag complexes and phosphines are tested (table 1.1). The results indicate that phosphines deliver exclusively the undesired S_N2 products, while NHC-Ag complexes have comparatively better S_N2' selectivity. By tuning the substitution patterns on the NHCs, different enantiomeric ratios can be achieved. NHC containing a mestiyl group with a mono-phenyl backbone **N5** showed the highest enantioselectivity (84:16 e.r.) with 56% yield of **1.11** after oxidation (entry 5).

Table 1.1 Ligand Screening for the Enantioselective Allylic Substitution With Diborylmethane **1.2**







N1 Ar = Mes
N2 Ar = 2,6-$Et_2C_6H_3$
N3 Ar = 2,4,6-iPr$_3C_6H_2$
N4 Ar = 2-Me,6-iPrC_6H_3
N8 Ar = 3,5-tBu$_2C_6H_3$
N9 Ar = 3,5-Trip$_2C_6H_3$
N10 Ar = 5-tBu,2-MeC_6H_3
N11 Ar = 5-tBu,2-PhC_6H_3
N12 Ar = 5-tBu,2-(3,5-$Me_2C_6H_3$)C_6H_3

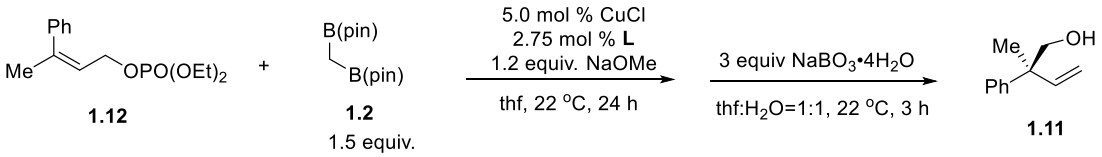
N5 Ar = Mes
N6 Ar = 2,6-$Et_2C_6H_3$
N7 Ar = 2,4,6-iPr$_3C_6H_2$

Entry	Ligand	Conv. %[b]	S_N2':S_N2[c]	Yield %[d]	e.r.[e]
1	**N1**	88	93:7	74	78:22
2	**N2**	75	83:17	38	75:25
3	**N3**	71	5:95	ND	NA
4	**N4**	62	58:42	33	74:26
5	**N5**	72	93:7	56	84:16
6	**N6**	79	93:7	69	81:19
7	**N7**	65	39:61	25	68:32
8	**N8**	74	61:39	36	44:56
9	**N9**	84	48:52	33	20:80
10	**N10**	72	98:2	60	38:62
11	**N11**	73	98:2	52	36:64
12	BINAP[f]	52	<2:>98	ND	NA
13	dppp[f]	63	<2:>98	ND	NA
14	SIMes[f]	24	<2:>98	ND	NA

[a] Reactions were performed under N_2 atmosphere. [b,c] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [d] Isolated yield after oxidation. [e] Determined by HPLC analysis. [f] 5.5 mol % of ligand used.

We then investigated a variety of ligands for the the addition to *Z*-allylic phosphate **1.12**, since the allylic substitution would generate the same product. As shown in table 1.2, to our delight, complexes with 3,6-substituted N-Aryl group would lead to higher enantioselectivity (90:10 e.r. and 92:8 e.r., entry 7,8), although ligands with other substituted patterns afford lower e.r. Among them, **N12** promotes an efficient reaction with 98:2 S_N2':S_N2 selectivity, 80% yield and 92:8 e.r.

Table 1.2 Ligand Screening Enantioselective Allylic Substitution With Diboron Reagents



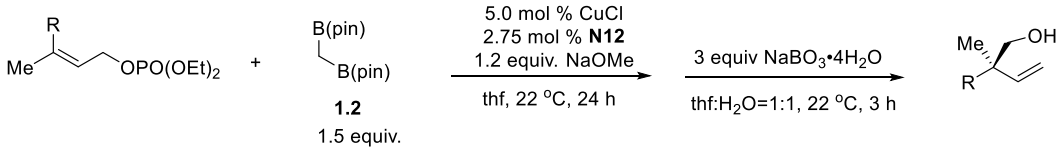
Entry	Ligand	Conv. %[b]	S_N2':S_N2[c]	Yield %[d]	e.r.[e]
1	**N1**	68	67:33	25	67:33
2	**N5**	67	81:19	38	62:38
3	**N7**	70	25:75	13	64: 36
4	**N8**	80	3:97	ND	ND
5	**N9**	72	19:81	12	54:46
6	**N10**	70	57:43	36	76:24
7	**N11**	86	93:7	76	90:10
8	**N12**	98	98:2	80	92:8
9[f]	**N11**	<5	NA	NA	NA

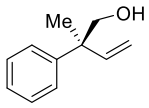
[a] Reactions were performed under N_2 atmosphere. [b,c] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [d] Isolated yield after oxidation. [e] Determined by HPLC analysis. [f] Without CuCl.

1.4 SCOPE OF CATALYTIC ENANTIOSELECTIVE ALLYLIC SUBSTITUTION WITH A DIBORYLMETHANE REAGENT

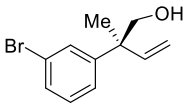
With the optimized conditions in hand, we explored the scope of the enantioselective allylic substitution with diborylmethane **1.2**. As shown in scheme 1.5, halogen-containing substrates are well tolerated (**1.11b**, **1.11c**, **1.11g**). Allylic phosphates bearing electron-rich and electron-poor arenes are also suitable substrates (**1.11d**, **1.11e)**. Sterically-demanding substrate with o-OMe substituent **1.11f** works well, with a slightly lower efficiency (79% yield and 95:5 e.r.). Alkyl allylic phosphate **1.11h** also works well but with a moderate enantiomeric ratio (84:16 e.r.), probably due to the difficulty in differentiating an alkyl group with a methyl group. Additions to most of these substrates afford excellent S_N2' selectivities (≥ 98:2), except for electron-deficient p-CF_3 containing **1.11d** (85:15), probably because the higher reactivity makes the energetic difference between the desired pathway and the background reaction that leads to S_N2 product is smaller.

Scheme 1.5 Scope of Enantioselective Allylic Substitution With Diboron Reagents

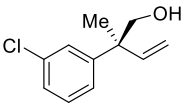




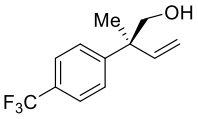
1.11
88% conv., 80% yield,
98:2 S_N2':S_N2, 92:8 e.r.



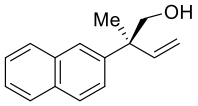
1.11b
90% conv., 78% yield,
98:2 S_N2':S_N2, 95:5 e.r.



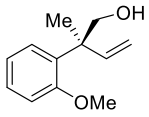
1.11c
83% conv., 69% yield
98:2 S_N2':S_N2, 94.5:5.5 e.r.



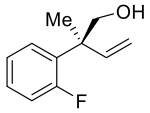
1.11d
96% conv., 70% yield,
85:15 S_N2':S_N2, 95:5 e.r.



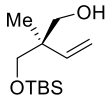
1.11e
70% conv., 67% yield,
>98:2 S_N2':S_N2, 94:6 e.r.



1.11f[a,b,c]
86% conv., 79% yield,
98:2 S_N2':S_N2, 95:5 e.r.



1.11g[a,b,d]
82% conv., 67% yield,
98:2 S_N2':S_N2, 91:9 e.r.



1.11h[b]
94% conv., 86% yield,
98:2 S_N2':S_N2, 84:16 e.r.

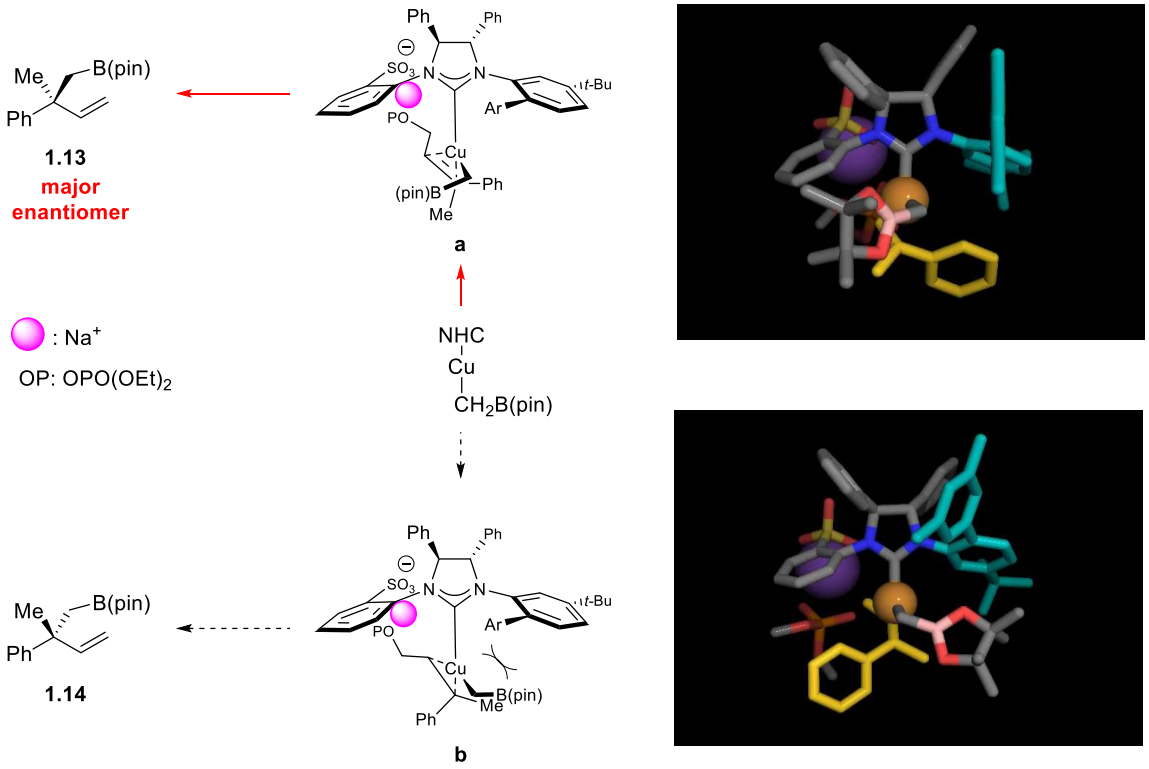
[a] 7.5 mol % CuCl, 4.1 mol % ligand used. [b] **N11** used instead of **N12**. [c] 96 h instead of 24 h. [d] 48 h instead of 24 h. [e] Isolated yield of pure S_N2' product.

1.5 STEREOCHEMICAL MODEL FOR CATALYTIC ENANTIOSELECTIVE ALLYLIC SUBSTITUTION WITH A DIBORYLMETHANE REAGENT

We then envisioned a stereochemical model for the enantioselective allylic substitution which accounts for the observed enantioselectivity. As shown in scheme 1.6,

the extended bulky Ar group on the NHC would push the B(pin) moiety away from itself, which favors pathway a. The difference between the two substituents with B(pin) (Ph vs Me) accounts for the generation of the major enantiomer **1.13**. Mechanistic rationale accounting for the better performance of *Z* vs *E* substrates requires further study.

Scheme 1.6 Stereochemical Model for Enantioselective Allylic Substitution

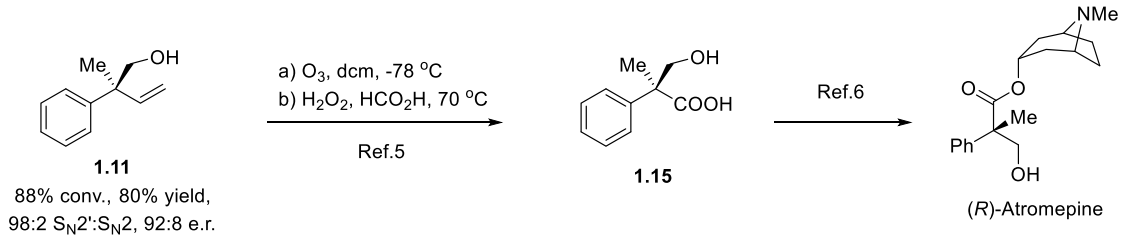


1.6 APPLICATION IN FORMAL SYNTHESIS OF BIOACTIVE MOLECULES

The terminal olefin and pinacolboronic ester group presented in the products of enantioselective allylic substitution provide a potential for conversion to a variety of valuable intermediates in the synthesis of natural products and pharmaceuticals. For

example, oxidation of compound **1.11** with ozone and hydrogen peroxide produced (*R*)-α-methyltropic acid **1.15**,[5] which is a key intermediate for the synthesis of (*R*)-Atromepine, a drug treating heart rhythm disease (scheme 1.7).[6] Our method generates the desired compound **1.11** in higher yield and enantiomeric ratio than previous reports.[5]

Scheme 1.7 Formal Synthesis of (*R*)-Atromepine



1.7 CONCLUSION

We have developed a catalytic method for enantio- and S_N2'-selective allylic substitution of commercially available diborylmethane to trisubstituted allylic phosphates. The transformations are catalyzed by NHC–Cu complexes. Products bearing quaternary stereogenic carbon centers are obtained in up to 86% yield (after oxidation), >98:2 S_N2':S_N2 selectivity and 95:5 enantiomeric ratio. We applied this method in the formal synthesis of bioactive molecule (*R*)-Atromepine. Further studies on expanding substrate scope, mechanistic studies, functionalization of products and application towards the synthesis of valuable compounds are in progress.

(5) Zhang, Q.; Zhu, S.; Cai, Y.; Wang, L.; Zhang, Q. *Sci China Chem*, **2010**, *53*, 1899-1906.
(6) Melone G.; Vecchi A.; Pagani G.; Testa E. *J. Org. Chem.* **1960**, *25,* 859–861.

1.8 EXPERIMENTAL

General

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, νmax in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet, app. = apparent), and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm). High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralpak AZ–H (5.0 × 250 mm), Chiralpak OD–H (5.0 × 250 mm)) in comparison with authentic racemic materials. Specific rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column; CH_2Cl_2

and Et_2O were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich Chemical Co.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific) in air.

Reagents and Ligands

Allylic phosphates: prepared according to previously reported methods.[7,8]

Bis[(pinacolato)boryl]methane (1.2): prepared according to previously reported methods.[9]

Copper (I) chloride: purchased from Strem Chemicals Inc. and used as received.

Diethyl chlorophosphate: purchased from Aldrich and used as received.

NHC–Ag complexes: prepared following previously reported methods.[10]

Sodium perborate tetrahydrate: purchased from Aldrich and used as received.

Sodium methoxide: purchased from Strem Chemicals Inc. and used as received.

Triethylamine: purchased from Fisher Scientific, Inc. and distilled over CaH_2 prior to use.

Representative Procedure for Cu(I)-Catalyzed Enantioselective Allylic Substitution with Diboron Reagents:

An oven-dried 1 dram vial equipped with a stir bar was charged with NHC-Ag

(7) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **2012**, *134*, 1490–1493.
(8) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.*, **2014**, *79*, 2354–2367.
(9) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537.
(10) (a) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 419–423.

complex **N12** (4.0 mg, 2.75 μmol) and CuCl (0.5 mg, 5 μmol) in a nitrogen-filled glove box. Freshly distilled THF (0.8 mL) was added to the vial and the mixture was allowed to stir at 22 °C for 2 h. After that, NaOMe (6.5 mg, 120 μmol) was added and the vial was sealed with a cap (phenolic open top cap with a red PFTE/white silicon septum) and electrical tape, and removed from the glove box. The solution of allylic phosphate (28.4 mg, 0.10 mmol) and diborylmethane **1.2** (40.2 mg, 0.15 mmol) in THF (0.3 mL) was added to the reaction mixture through a plastic syringe and the resulting mixture was allowed to stir at 22 °C for 24 h.

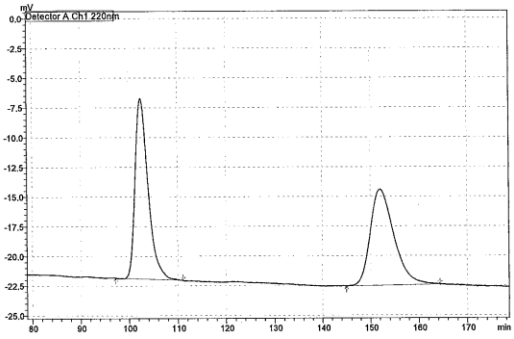
The mixture was passed through a short plug of silica gel and eluted with Et_2O. The organic layer was concentrated *in vacuo*, and then $NaBO_3 \bullet 4H_2O$ (46.2 mg, 0.30 mmol), THF (1 mL) and H_2O (1 mL) was added to the same vessel. The mixture was allowed to stir at 22 °C for 3 h. The mixture was extracted with Et_2O and concentrated to give colorless oil, which was purified by silica gel chromatography to afford the desired product as colorless oil.

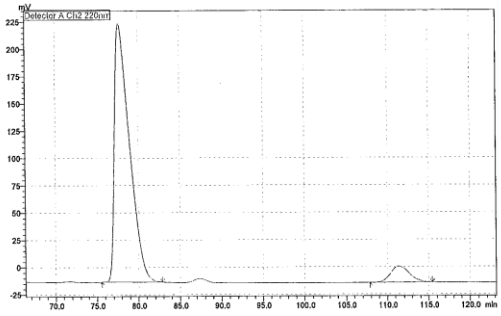
(*S*)-2-Methyl-2-phenylbut-3-en-1-ol (1.11):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.24 (5H, m), 6.08 (1H, dd, *J* = 17.6, 10.8 Hz), 5.28 (1H, dd, *J* = 10.8, 1.2 Hz), 5.16 (1H, dd, *J* = 17.6, 1.2 Hz), 3.80 (2H, d, *J* = 6.4 Hz), 1.44 (3H, s), 1.35 (1H, br s). The ^{1}H NMR matches previous report.[11] Specific rotation: $[\alpha]_D^{20}$ 16.3 (c 1.0, EtOH) for an enantiomerically enriched sample of 92:8 e.r., and absolute configuration assigned as *S*.[5]

(11) Ngai, M. Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 99.5:0.5 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.





Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	102.487	2803158	15200	50.276		M
2	152.128	2772407	8102	49.724		M
Total		5575565	23303			

<Peak Table>

Detector A Channel 2 220nm

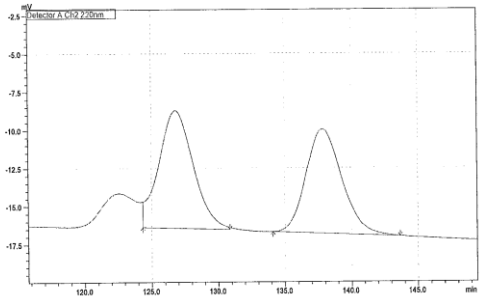
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	77.702	29943431	236509	92.769		M
2	111.390	2334137	14768	7.231		M
Total		32277567	251276			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	102.487	50.276	1	77.702	92.769
2	152.128	49.724	2	111.390	7.231

(*S*)-2-(3-Bromophenyl)-2-methylbut-3-en-1-ol (1.11b):

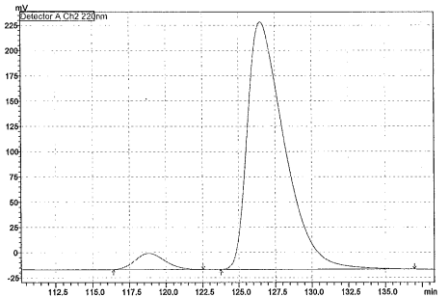
IR (neat): 3392 (br), 2969 (m), 2932 (m), 2875 (m), 1592 (m), 1562 (s), 1474 (s), 1416 (s), 1071 (s), 1041 (s), 997 (s), 921 (s), 783 (s), 747 (s), 699 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (1H, t, J = 1.6 Hz), 7.37-7.34 (1H, m), 7.29-7.24 (1H, m), 7.19 (1H, t, J = 4.0 Hz), 6.01 (1H, ddd, J = 17.6, 10.8, 1.2 Hz), 5.28 (1H, dd, J = 10.8, 1.2 Hz), 5.14 (1H, d, J = 17.6 Hz), 3.75 (2H, d, J = 1.6 Hz), 1.39-1.38 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.1, 142.8, 130.2, 129.9, 129.6, 125.6, 122.7, 115.2, 69.7, 47.0, 22.6; HRMS (ESI^+): Calcd for $C_{11}H_{12}Br$ $[M+H-H_2O]^+$: 223.0112; Found: 223.0132. Specific rotation: $[\alpha]_D^{20}$ 9.8 (c 1.0, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 99.5:0.5 hexanes/*i*PrOH, 0.5 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	126.803	1383723	7711	51.884		M
2	137.815	1283255	6817	48.116		M
Total		2666978	14528			



<Peak Table>
Detector A Channel 2 220nm

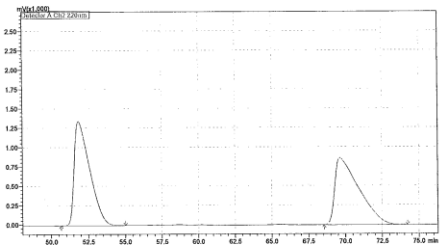
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	118.804	2222583	15767	4.924		M
2	126.492	42916132	244825	95.076		M
Total		45138715	260591			

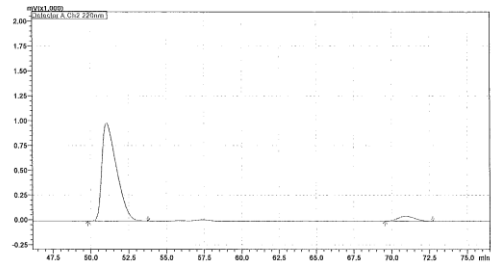
Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	126.803	51.884	1	118.804	4.924
2	137.815	48.116	2	126.492	95.076

(*S*)-2-(3-Chlorophenyl)-2-methylbut-3-en-1-ol (1.11c):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.33 (1H, m), 7.27-7.22 (4H, m), 6.04 (1H, dd, *J* = 17.6, 10.8 Hz), 5.29 (1H, dd, *J* = 10.0, 1.2 Hz), 5.16 (1H, dd, *J* = 17.6, 1.2 Hz), 3.78 (2H, d, *J* = 6.8 Hz), 1.47-1.35 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 142.8, 134.4, 129.6, 127.4, 126.7, 125.1, 115.2, 69.7, 47.0, 22.6;

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 99.0:1.0 hexanes/*i*PrOH, 0.5 mL/min, 220 nm.





<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	N
1	51.852	98053732	1345448	49.853		M	
2	69.645	98630687	864933	50.147		M	
Total		196684419	2210381				

<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	51.050	66417653	991775	94.527		M	
2	70.920	3845228	49871	5.473		M	
Total		70262881	1041646				

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	51.852	49.853	1	51.050	94.527
2	69.645	50.147	2	70.920	5.473

(*S*)-2-Methyl-2-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (1.11d):

IR (neat): 3380 (br), 2970 (w), 2936 (w), 1618 (w), 1412 (w), 1372 (s), 1165 (s), 1123 (s), 1067 (s), 1016 (s), 922 (s), 838 (m), 706 (w), 606 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (2H, d, J = 7.6 Hz), 7.47 (2H, d, J = 7.6 Hz), 6.04 (1H, dd, J = 18.0, 10.4 Hz), 5.30 (1H, d, J = 10.8 Hz), 5.14 (1H, d, J = 17.6 Hz), 3.80 (2H, s), 1.43 (3H, s), 1.40 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.8 (J = 2 Hz), 142.7, 128.7 (q, J = 32 Hz), 127.4, 125.5-125.2 (m), 122.8, 120.1, 115.5, 69.6, 47.1, 22.7; HRMS (ESI^+): Calcd for $C_{12}H_{12}F_3$ $[M+H-H_2O]^+$: 213.0891; Found: 213.0884. Specific rotation: $[\alpha]_D^{20}$ 7.4 (c 1.0, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r.

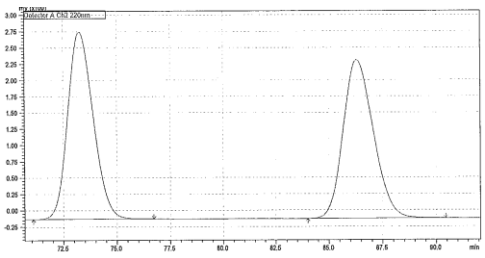
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 99.5:0.5 hexanes/*i*PrOH, 0.5 mL/min, 220 nm. Retention time: 66.49 min (major), 73.47 (minor).

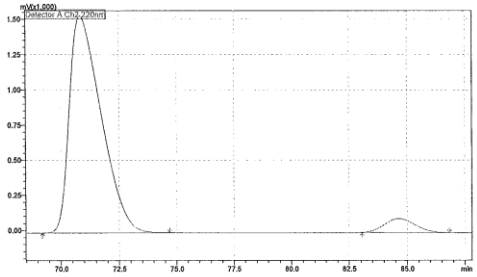
(*S*)-2-Methyl-2-(naphthalen-2-yl)but-3-en-1-ol (1.11e):

^1H NMR ($CDCl_3$, 500 MHz): δ 7.83-7.79 (4H, m), 7.51-7.46 (3H, m), 6.17 (1H, dd, J = 18.0, 11.0 Hz), 5.33 (1H, d, J = 11.0 Hz), 5.20 (1H, d, J = 17.5 Hz), 3.90 (2H, s), 1.54

(3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 141.8, 133.4, 132.1, 128.1, 128.0, 127.4, 126.1, 125.8, 125.6, 125.3, 114.9, 69.9, 47.2, 22.7.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 99.0:1.0 hexanes/*i*PrOH, 0.5 mL/min, 220 nm.





<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	73.261	23793941	287528	49.915		M	
2	86.304	23874689	243798	50.085		M	
Total		47668630	531326				

<Peak Table>
Detector A Channel 2 220nm

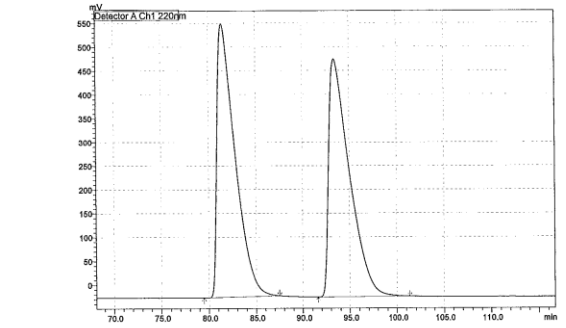
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	70.831	145631356	1540613	94.074		M
2	84.634	9173620	99277	5.926		M
Total		154804976	1639890			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	73.261	49.915	1	70.831	94.074
2	86.304	50.085	2	84.634	5.926

(*S*)-2-(2-Methoxyphenyl)-2-methylbut-3-en-1-ol (1.11f):

IR (neat): 3421 (br), 2936 (w), 2881 (w), 1598 (w), 1498 (s), 1462 (m), 1434 (m), 1240 (s), 1027 (s), 914 (m), 753 (s), 700 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (1H, dd, *J* = 8.0, 1.6 Hz), 7.24-7.20 (1H, m), 6.94-6.88 (2H, m), 6.20 (1H, dd, *J* = 18.0, 10.4 Hz), 5.16 (1H, dd, *J* = 10.8, 1.2 Hz), 5.03 (1H, dd, *J* = 18.0, 1.2 Hz), 3.98-3.93 (1H, m), 3.89-3.84 (1H, m), 3.80 (3H, s), 1.44 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 144.0, 132.3, 129.1, 128.0, 120.7, 113.2, 111.9, 68.5, 55.2, 47.0, 21.7; HRMS (ESI$^+$): Calcd for $C_{12}H_{16}O_2$ $[M+H]^+$: 193.1229; Found: 193.123. Specific rotation: $[\alpha]_D^{20}$ 14.4 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r.

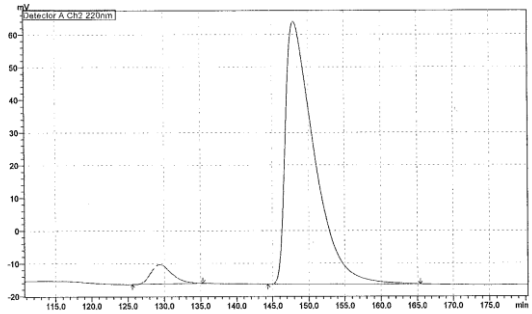
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 99.5:0.5 hexanes/*i*PrOH, 0.5 mL/min, 220 nm.



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	81.429	75521578	574415	49.825		M	
2	93.372	76051757	499454	50.175		M	
Total		151573335	1073869				



<Peak Table>

Detector A Channel 2 220nm

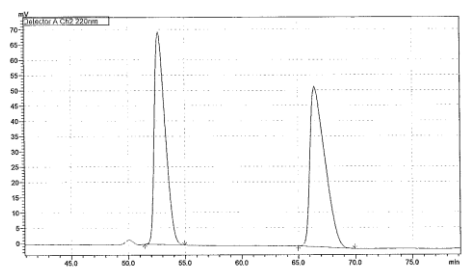
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	129.295	1200127	5958	5.136		M
2	148.027	22168539	80330	94.864		M
Total		23368666	86288			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	81.429	49.825	1	129.295	5.136
2	93.372	50.175	2	148.027	94.864

(*S*)-2-(2-Fluorophenyl)-2-methylbut-3-en-1-ol (1.11g):

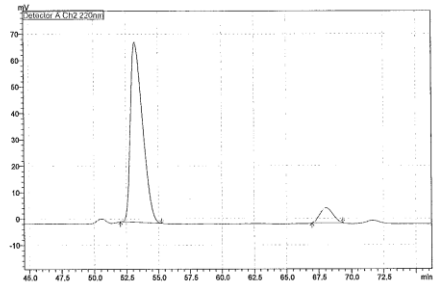
IR (neat): 3431 (br), 2926 (m), 2855 (w), 1598 (w), 1488 (m), 1447 (m), 1217 (m), 1039 (s), 919 (w), 809 (s), 756 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.34 (1H, m), 7.26-7.22 (1H, m), 7.12-7.09 (1H, m), 7.05-7.00 (1H, m), 6.14 (1H, dd, *J* = 17.5, 11.0 Hz), 5.26 (1H, d, *J* = 10.5 Hz), 5.09 (1H, d, *J* = 18.0 Hz), 3.89 (1H, d, *J* = 4.5 Hz), 1.48 (3H, s);

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 99.5:0.5 hexanes/*i*PrOH, 0.5 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	52.677	4559757	69541	48.825		M
2	66.453	4779296	52490	51.175		M
Total		9339054	122032			



<Peak Table>
Detector A Channel 2 220nm

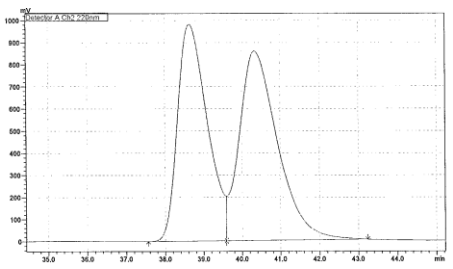
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	53.195	4487426	68180	91.974		M
2	68.077	391594	5712	8.026		M
Total		4879019	73892			

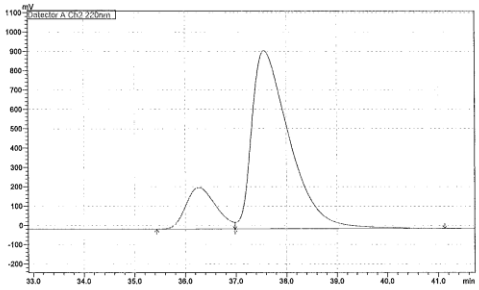
Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	52.677	48.825	1	53.195	91.974
2	66.453	51.175	2	68.077	8.026

(*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylbut-3-en-1-ol (1.11h):

IR (neat): 2927 (m), 1723 (s), 1470 (m), 1268 (s), 1096 (s), 1027 (m), 837 (s), 776 (m), 709 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.81 (1H, dd, J = 17.6, 10.8 Hz), 5.13 (1H, dd, J = 6.8, 1.2 Hz), 5.09 (1H, dd, J = 12.8, 1.2 Hz), 3.63-3.45 (4H, m), 2.52 (1H, br), 1.00 (3H, s), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 114.5, 70.4, 69.8, 43.0, 33.9, 29.7, 25.8, 18.4, 18.1, -5.7, -5.7; HRMS (ESI^+): Calcd for $C_{12}H_{15}OSi$ $[M+H-H_2O]^+$: 213.1675; Found: 213.168. Specific rotation: $[\alpha]_D^{20}$ 0.2 (c 1.0, $CHCl_3$) for an enantiomerically enriched sample of 84:16 e.r.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material of benzoate derivatives; Chiralpak OD–H column, 100% hexanes, 0.2 mL/min, 220 nm.





<Peak Table>

Detector A Channel 2 220nm

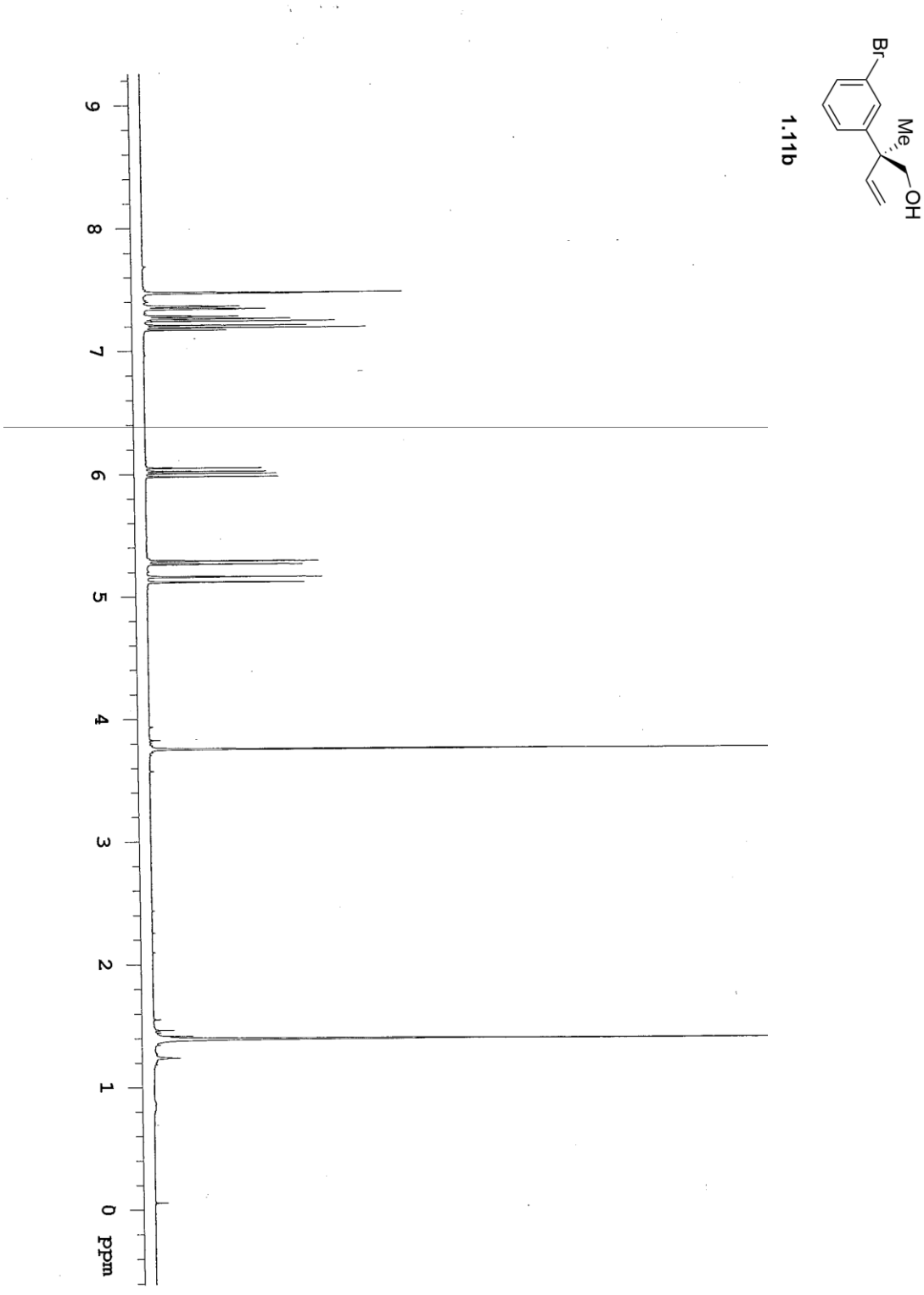
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	38.643	52778054	979613	47.222		M
2	40.337	58987079	856206	52.778		V M
Total		111765133	1835820			

<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	36.267	8858598	214575	15.701		M
2	37.567	47563137	922089	84.299		V M
Total		56421734	1136664			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	38.643	47.222	1	36.267	15.701
2	40.337	52.778	2	37.567	84.299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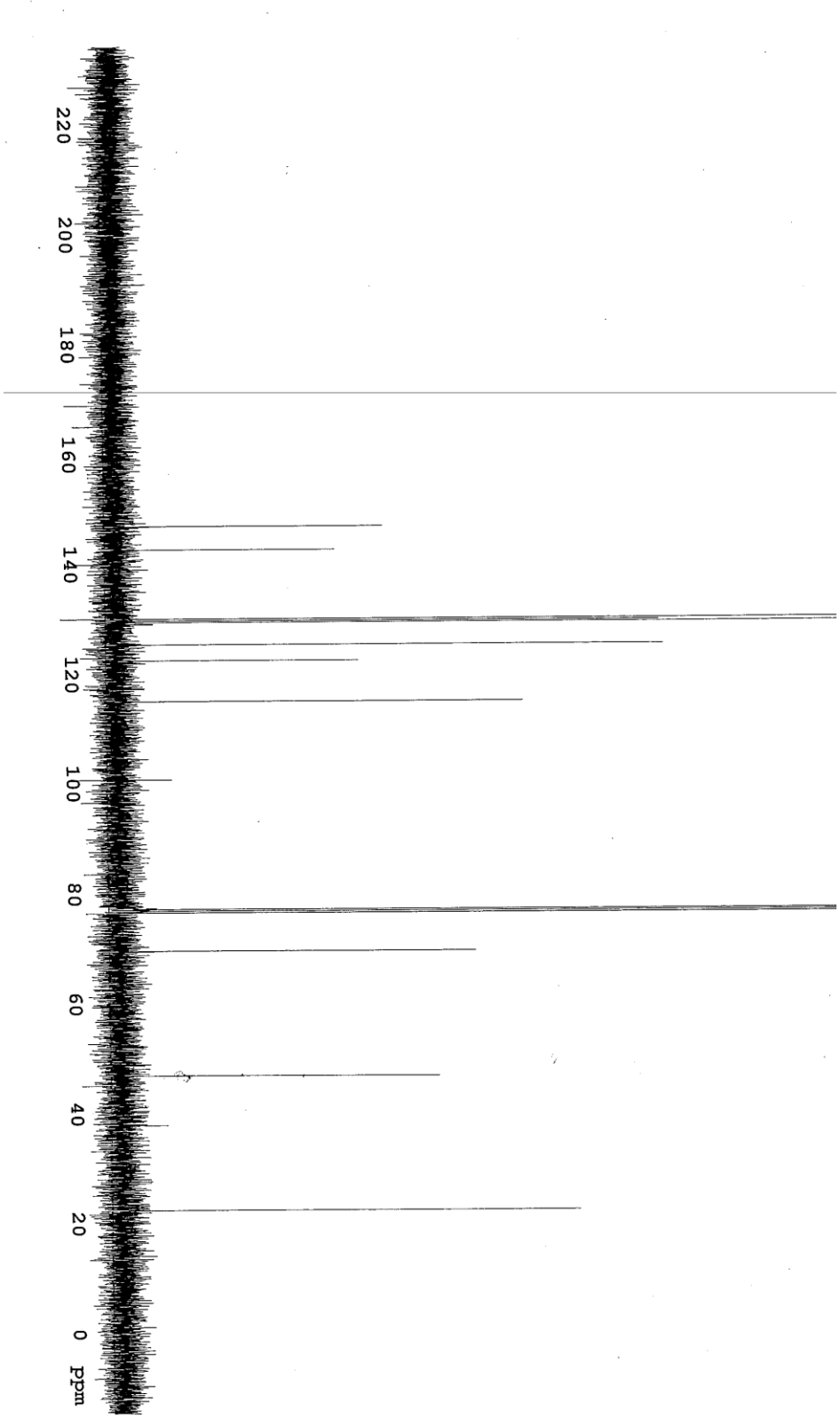
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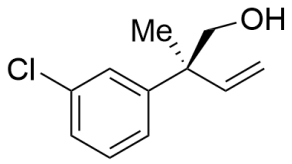

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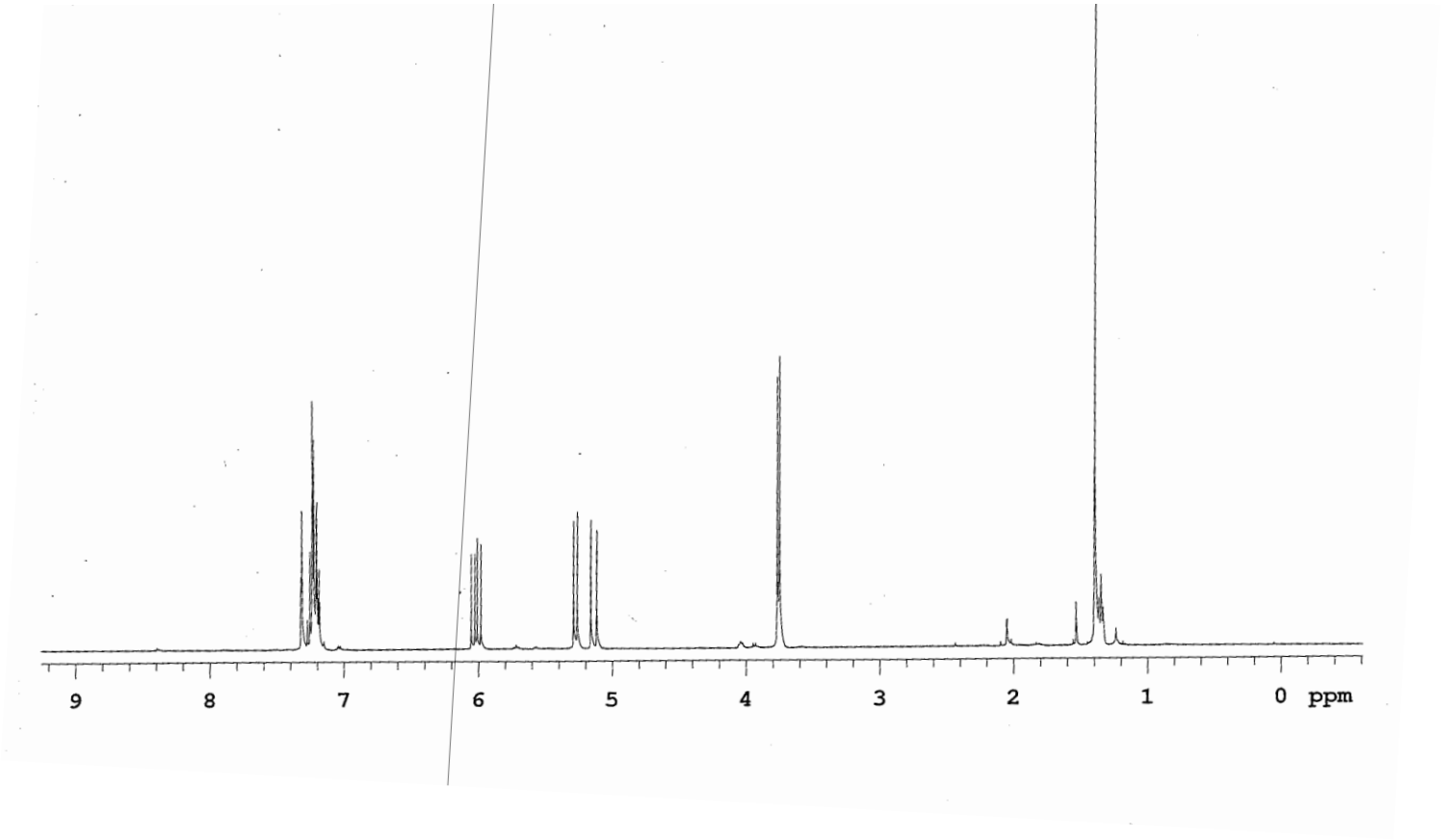

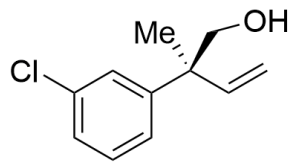

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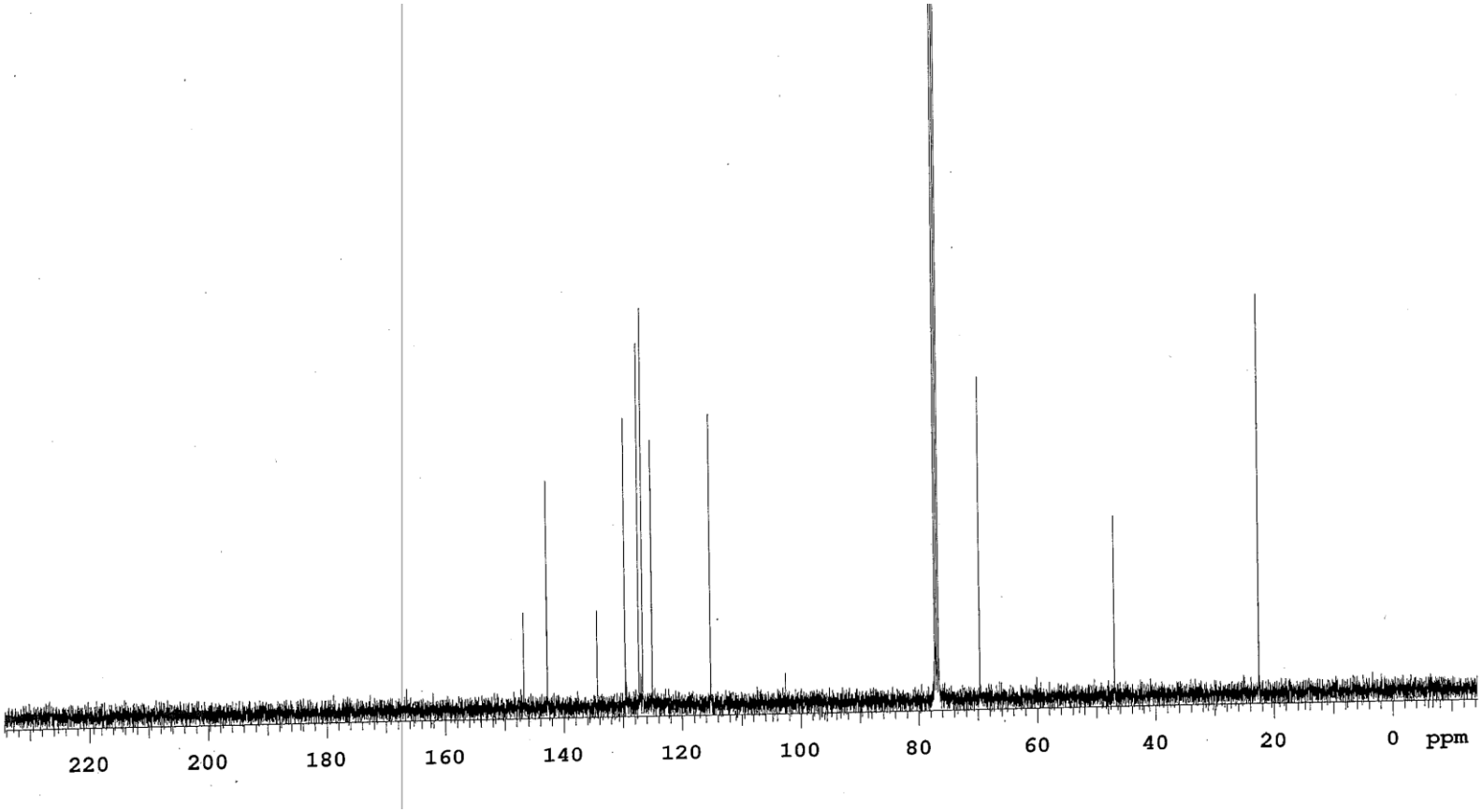

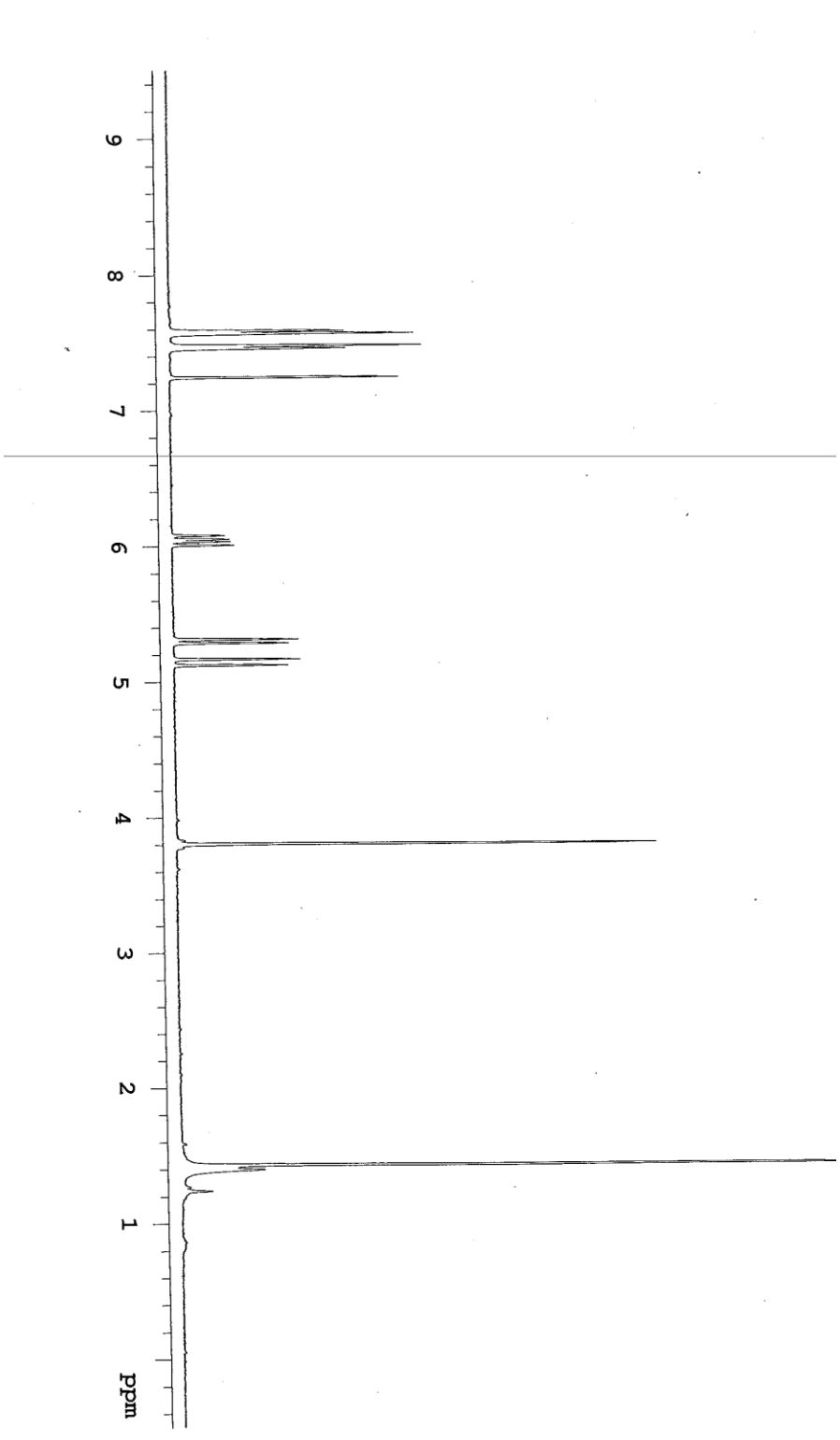
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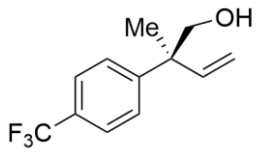

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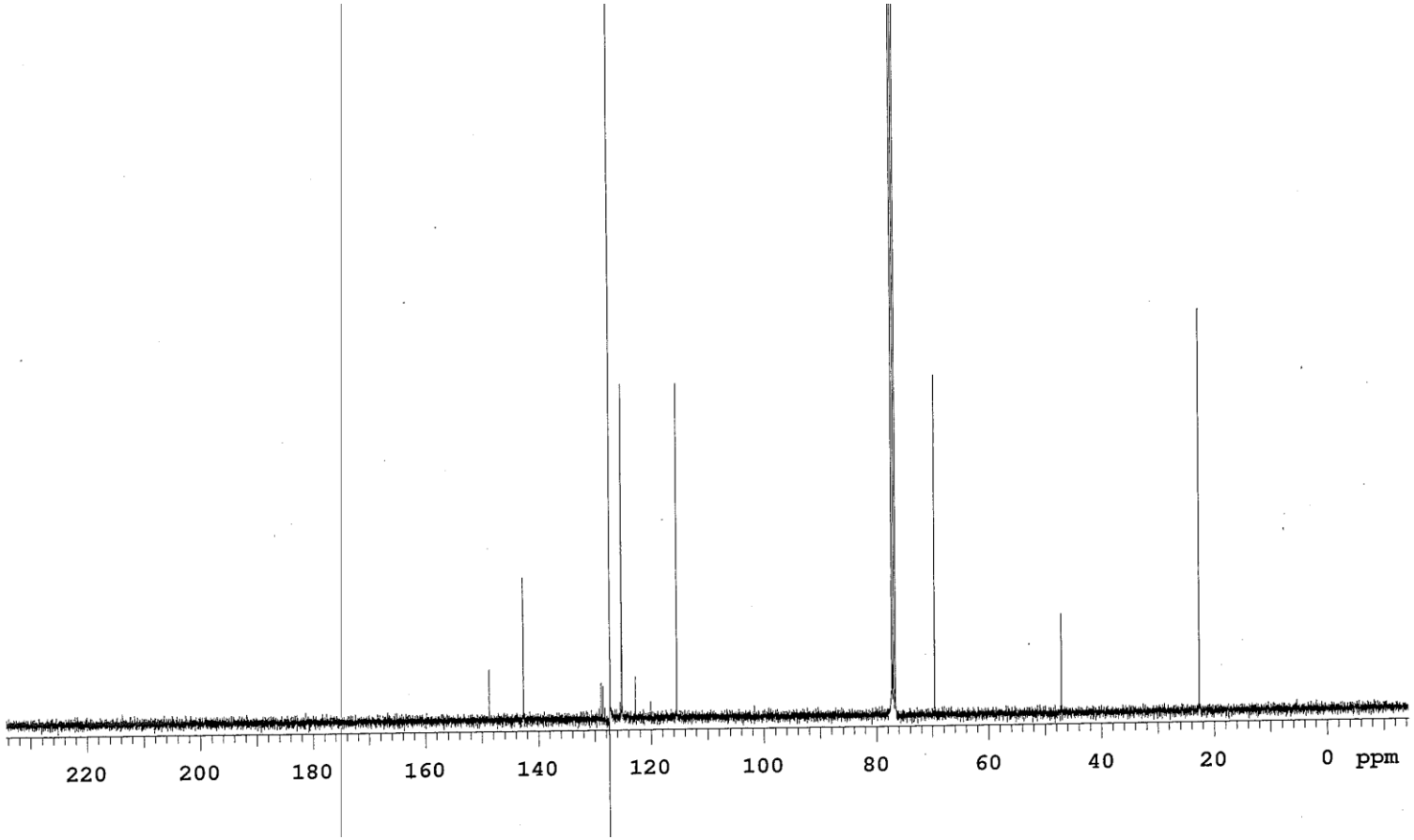

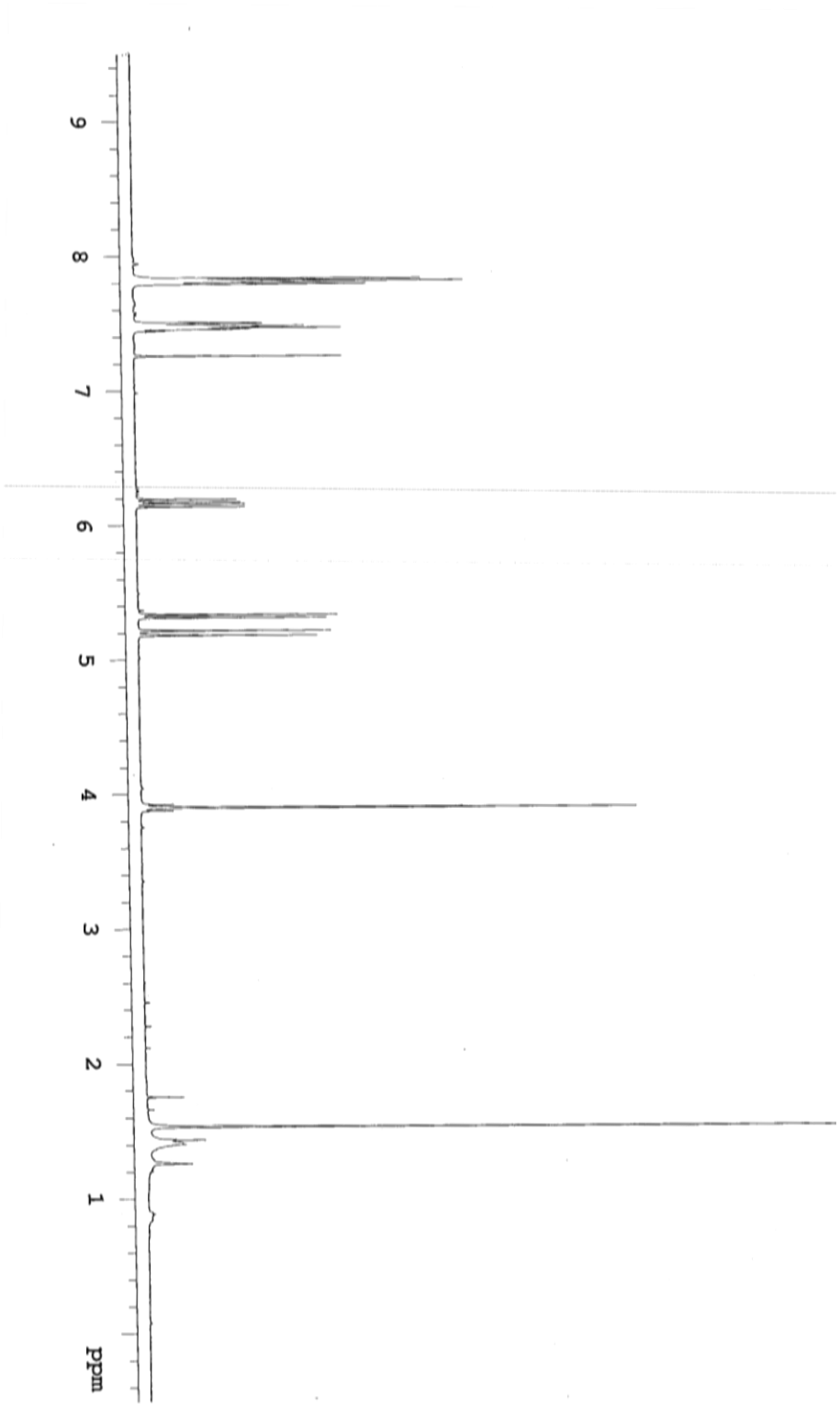
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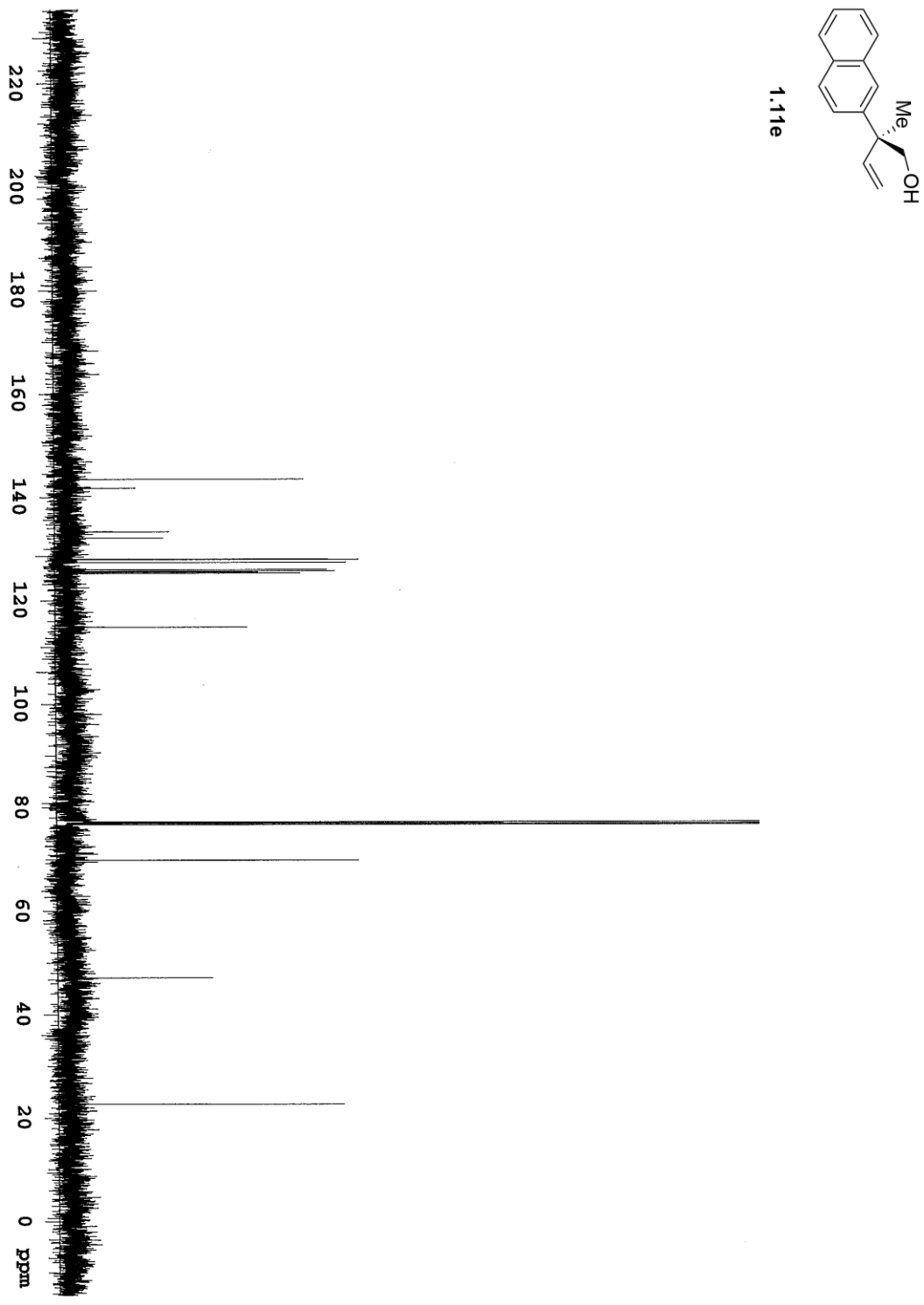
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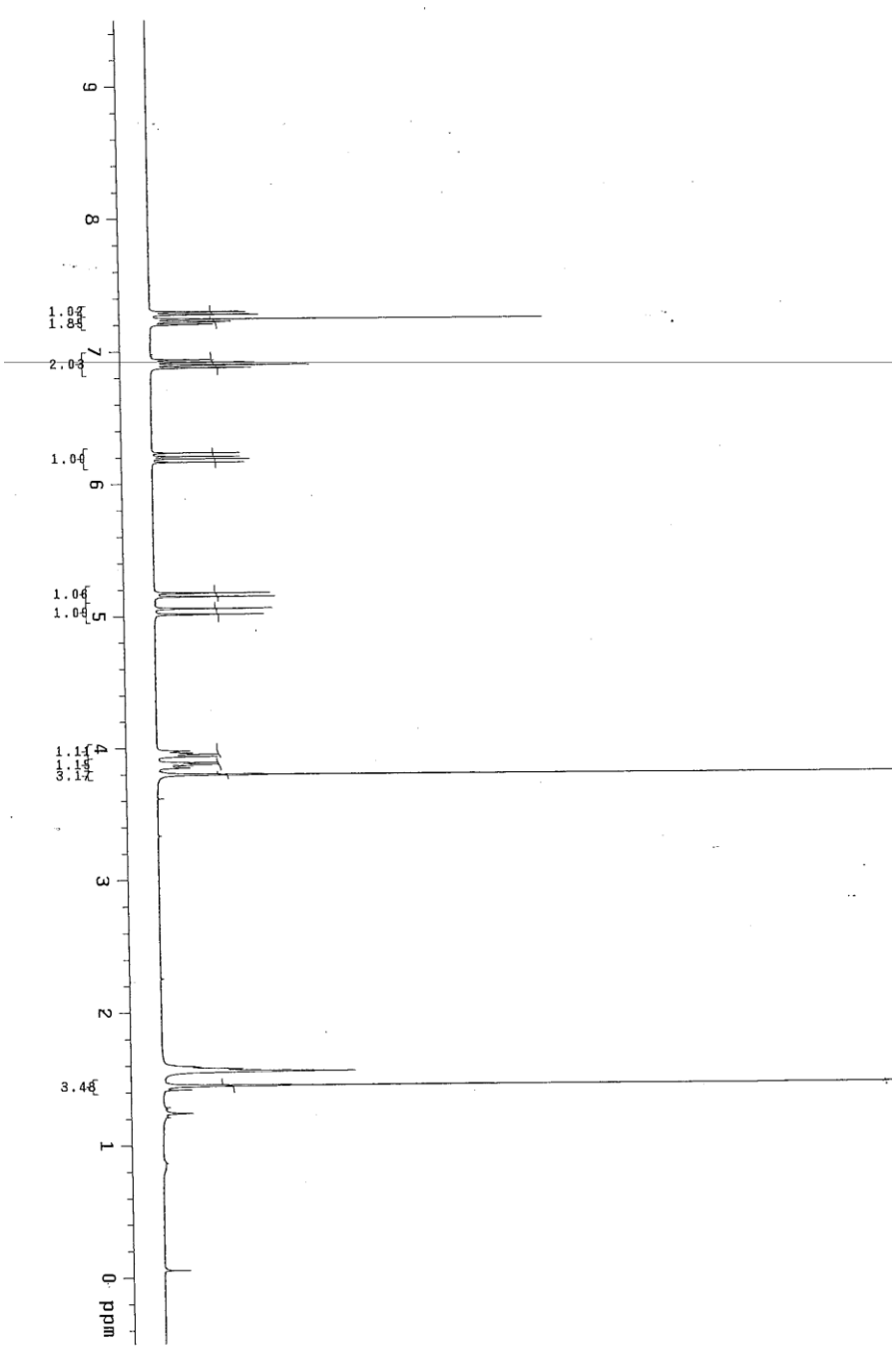
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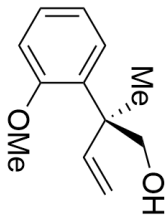
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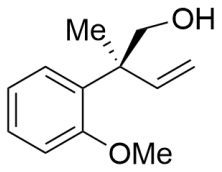
1.11f.



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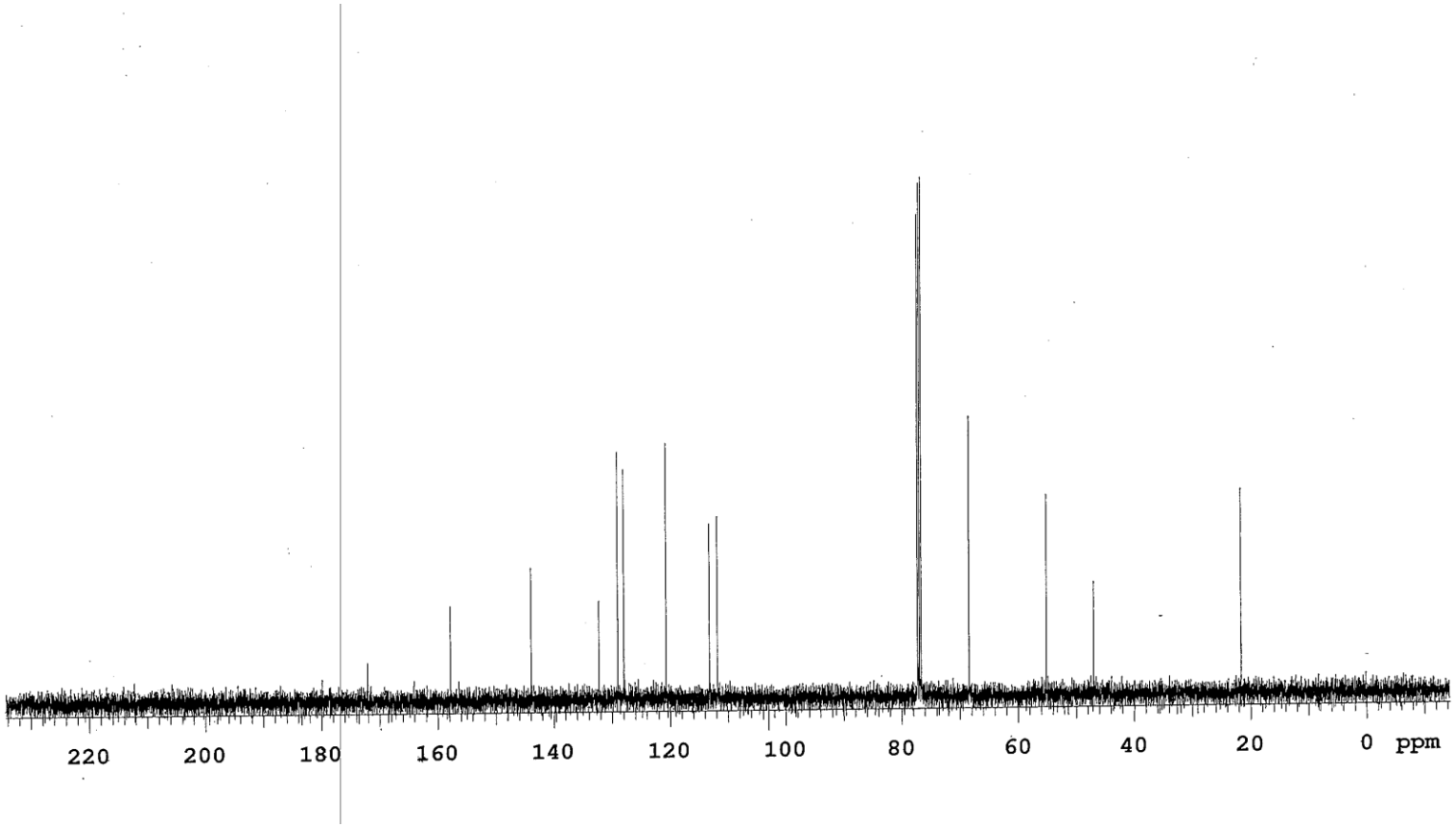
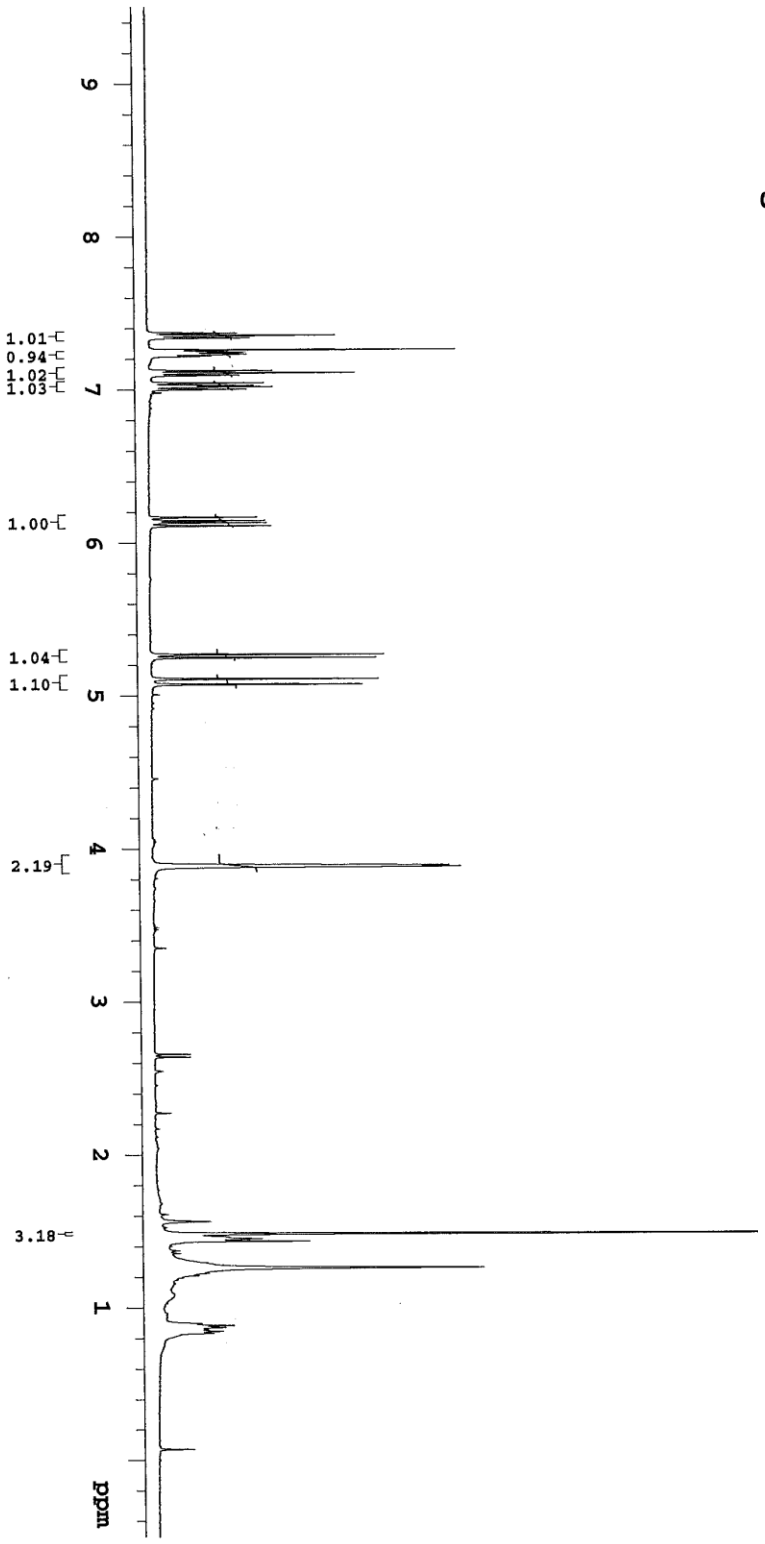
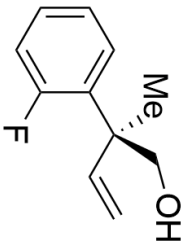
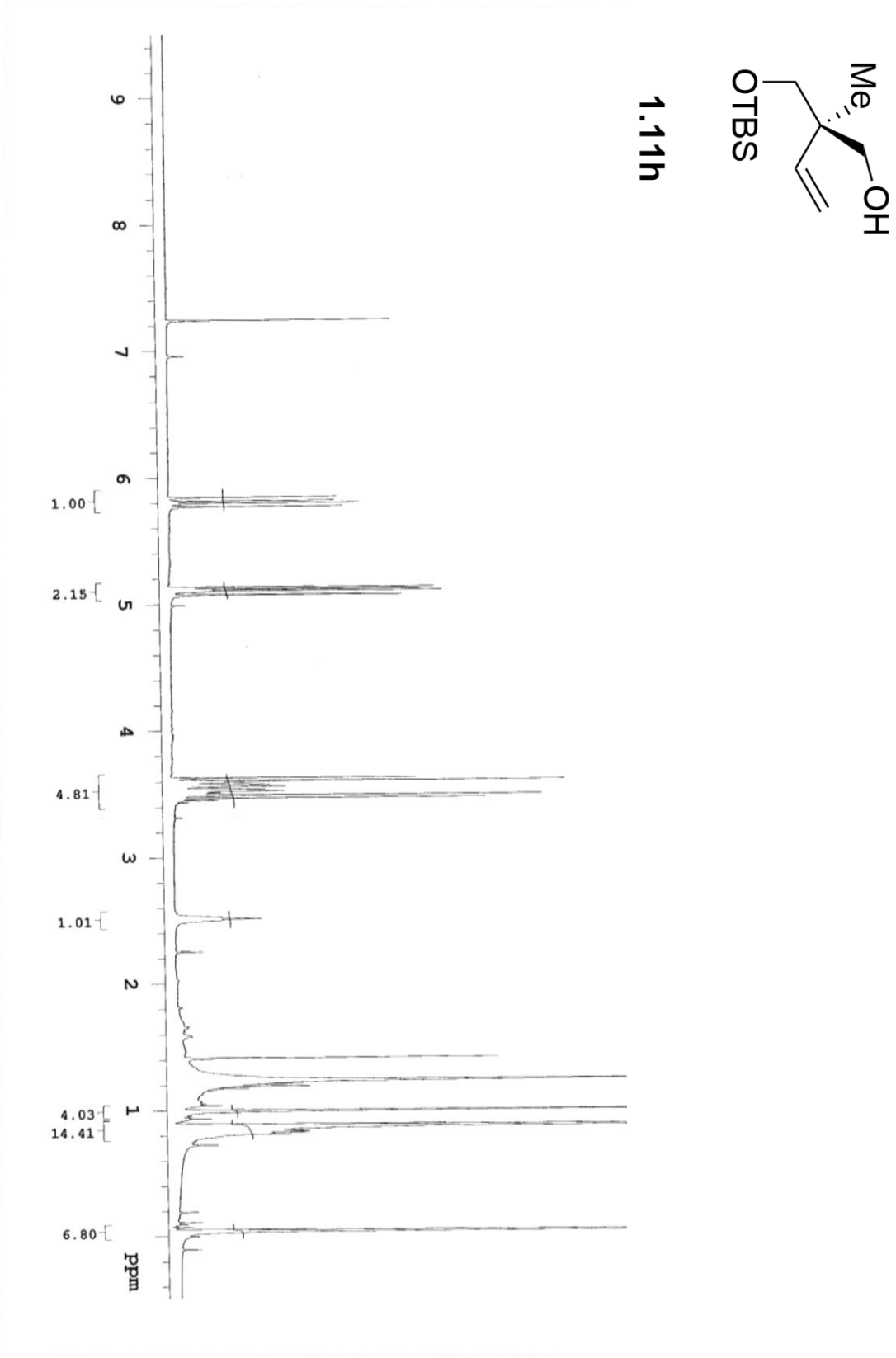






1.11g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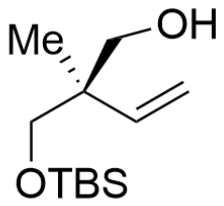

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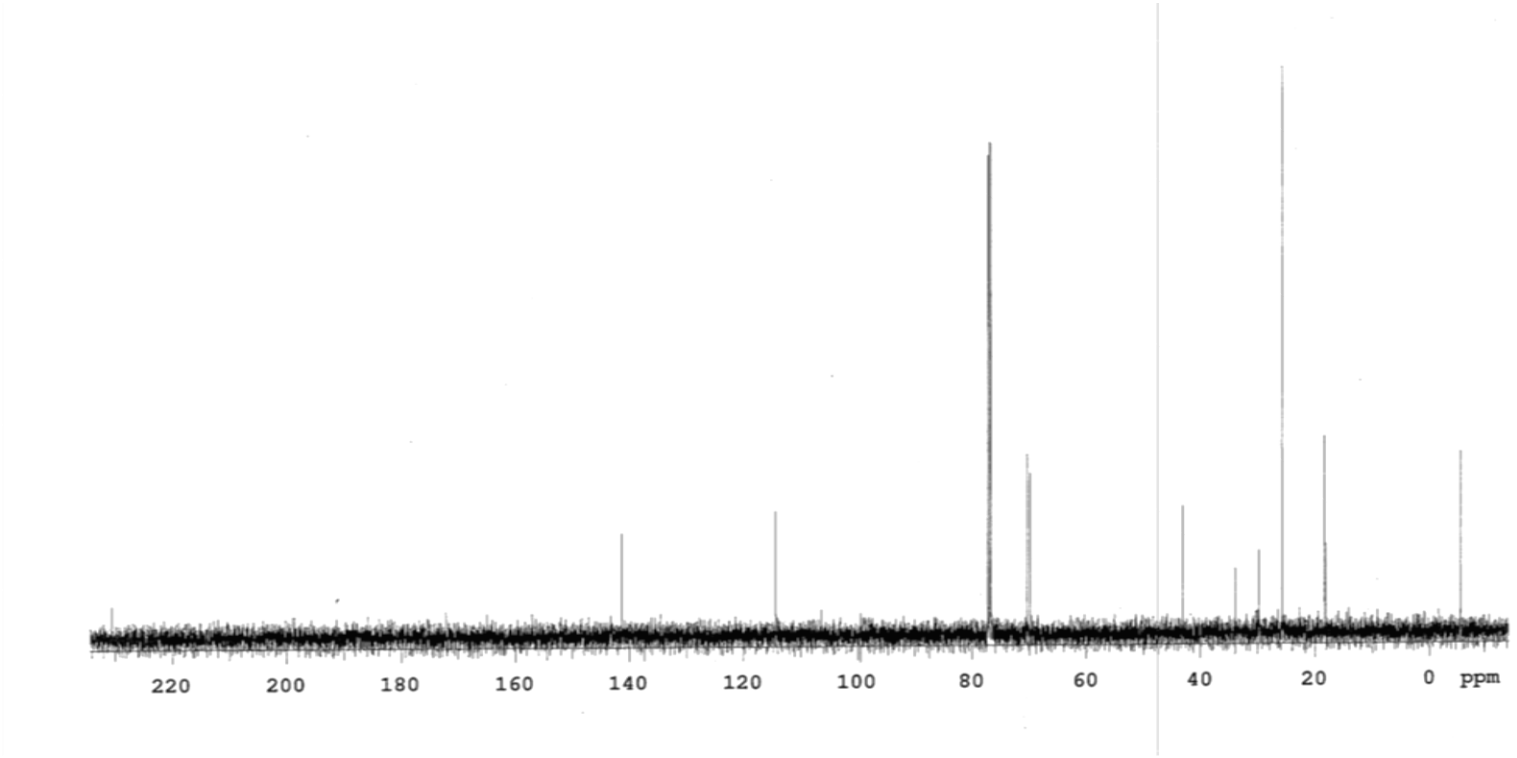


CHAPTER 2

CATALYTIC ENANTIOSELECTIVE MULTICOMPONENT ALLYL CONJUGATE ADDITION

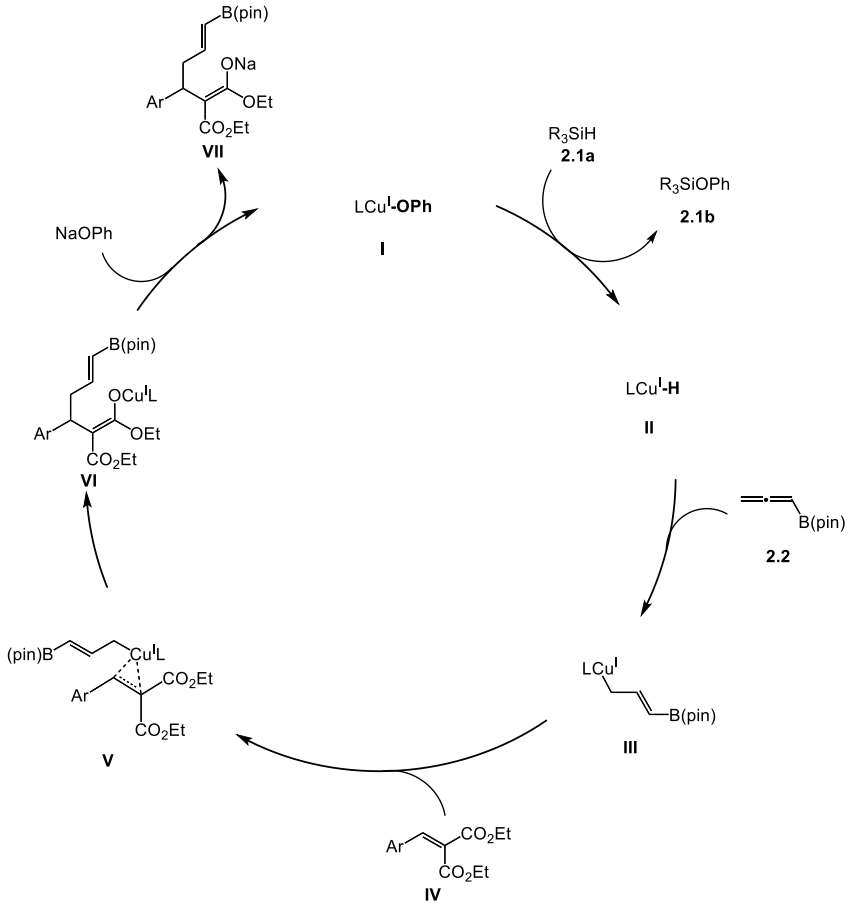
2.1 INTRODUCTION

Catalytic enantioselective conjugate additions are very important transformations in organic synthesis.[12] Many kinds of catalytic reactions are reported to transfer a variety of functional groups, such as aryl, alkenyl and alkyl groups, to the stereogenic center with high efficiency and enantioselectivity. Among these reports, catalytic enantioselective conjugate additions of allyl groups to α,β-unsaturated carbonyl compounds are rare. One challenging problem would be the undesired competitive background reactions caused by the ligand-free allylmetal species due to their high nucleophilicity. Another issue might be that stable π-allyl metal complexes do not easy to undergo reductive elimination.

(12) For reviews on catalytic enantioselective conjugate addition, see: (a) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852. (b) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075. (c) Cordova, A. *Catalytic Asymmetric Conjugate Reactions*; Wiley-VCH: Weinheim, **2010**. (d) Ji, J.-X.; Chan, A. S. C. *Catalyic Asymmetric Synthesis* (Ed.: I. Ojima); Wiley, Hoboken, **2010**, pp. 439–495.

Hoveyda group has recently reported catalytic enantioselective conjugate additions of propargyl and allyl groups. [13] We designed a catalytic multicomponent process (scheme 2.1) that begins with the formation of Cu-H species **II** from Cu^{I} alkoxide **I**, followed by Cu-H addition to allenyl-B(pin) to generate allylcopper intermediate **III**. The conjugate addition of allylcopper intermediate **III** to α,β-unsaturated malonate **IV** gives the intermediate **VI**, followed by ligand exchange to regenerate Cu^{I} alkoxide **I** and afford the desired conjugate addition product **VII**.

Scheme 2.1 Catalytic Cycle for Cu-Catalyzed Multicomponent 1,4-Conjugate Addition



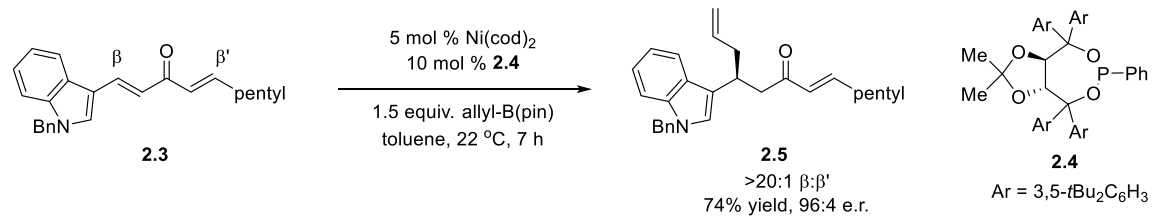
(13) (a) Meng, F.; Li, X., Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. *Nature*, **2016**, *537*, 387–393. (b) Li, X.; Meng, F.; Torker, S.; Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55,* 9997-10002.

A common problem for multicomponent reactions would be chemoselectivity issues in this process. For example, Cu alkoxide **I** can react with allenyl-B(pin) **2.2** to generate allenylcopper, which could participate in conjugate addition as well. Cu-H complex **II** can also directly add to α,β-unsaturated malonate **IV** to give reduction product. Besides all the aforementioned issues, allylcopper intermediate **III** could isomerize, which would generate linear & branched allylcopper, as well as *E*- & *Z*-isomers in a non-selective fashion. We hope to develop an efficient and enantioselective conjugate addition where side process can be minimized.

2.2 BACKGROUND

As for previous reports on enantioselective allyl conjugate addition, Morken and co-workers reported Ni-catalyzed enantioselective addition of allyl-B(pin) to dienone. (Scheme 2.2).[14] The reaction is very effective with dialkylidene ketones and favors the allylation of the benzylidene site in nonsymmetric substrates. The authors propose a mechanism involving an oxidative π-allyl formation and a 3,3'-reductive elimination process.

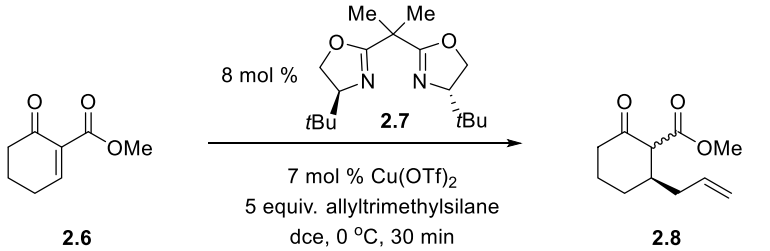
Scheme 2.2 Ni-Catalyzed Enantioselective Allyl Conjugate Addition



(14) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983.

In 2008, the Snapper group reported catalytic enantioselective Hosomi–Sakurai conjugate allylation of cyclic unsaturated ketoesters (Scheme 2.3).[15] Conjugate addition products can be generated in up to 78% yield and >98:2 e.r. with a bisoxazole-Cu complex.

Scheme 2.3 Catalytic Enantioselective Hosomi-Sakurai Allyl Conjugate Additions

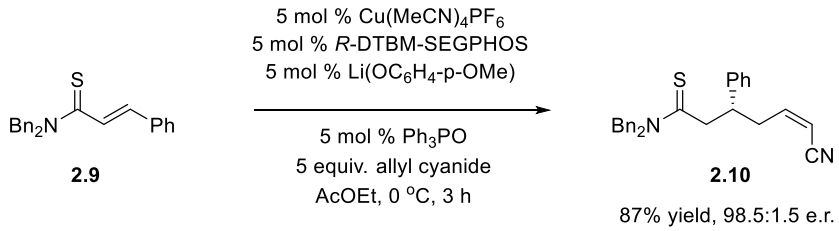


2.6 **2.8**

78% yield, 95:5 e.r.

In 2011, Shibasaki and co-workers reported the enantioselective conjugate addition of allyl cyanide to α,β-unsaturated thioamides **2.9** (Scheme 2.4).[16] Product **2.10** is obtained in 87% yield and 98.5:1.5 e.r.

Scheme 2.4 Cu-Catalyzed Enantioselective Conjugate Addition of Cyano-containing Allyl Group



2.9 **2.10**

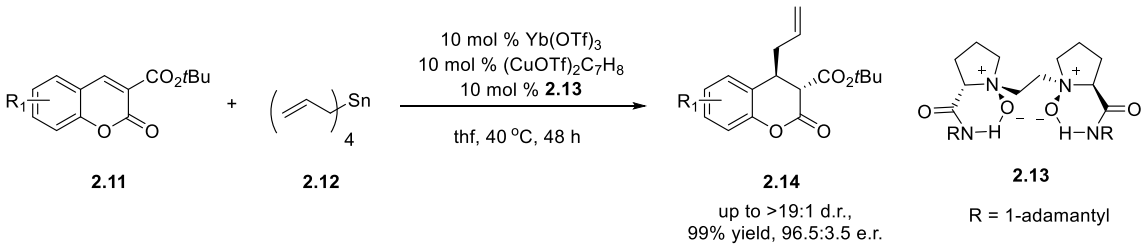
87% yield, 98.5:1.5 e.r.

In 2011, Feng and co-workers reported catalytic enantioselective conjugate allylation to coumarins (Scheme 2.5).[17] They employed a dual activation strategy by using N,N'-dioxide-Yb(OTf)$_3$ to activate coumarin **2.11**, and using (CuOTf)$_2$•C$_7$H$_8$ to

(15) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049–5051.
(16) Yanagida, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7910–7914.
(17) Kuang, Y.; Liu, X.; Chang, L.; Wang, M.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 3814–3817.

activate tetraallyltin **2.12** by transmetalation. Products are obtained in up to 99% yield, >19:1 d.r. and 96.5:3.5 e.r. under mild conditions.

Scheme 2.5 Catalytic Enantioselective Conjugate Allyl Adddition to Coumarins



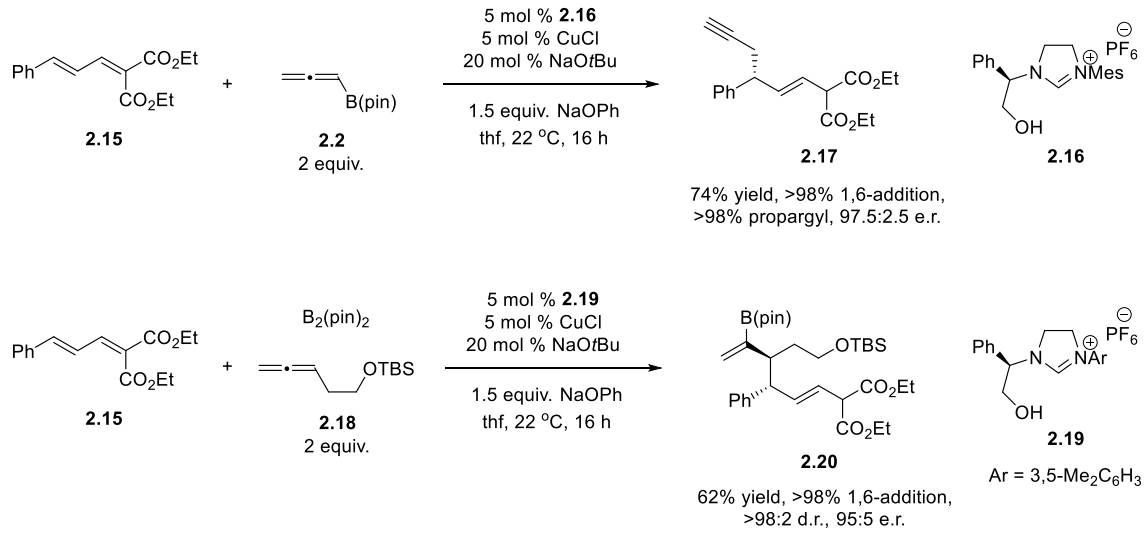
2.11 **2.12** **2.14** **2.13**

up to >19:1 d.r., 99% yield, 96.5:3.5 e.r.

R = 1-adamantyl

In 2016, Hoveyda and co-workers reported catalytic enantioselective 1,6-conjugate additions of allyl-type nucleophiles promoted by NHC–Cu complexes (Scheme 2.6).[13a] Propargyl and allyl 1,6-addition products are formed in high efficiencies, diastereo- and enantioselectivities. The author proposed that the transformations proceed through an unprecedented Cu-catalyzed 3,3'-reductive elimination.

Scheme 2.6 Catalytic Enantioselective 1,6-Conjugate Addition of Propargyl and Allyl Groups



2.15 **2.2** 2 equiv. **2.17** **2.16**

74% yield, >98% 1,6-addition, >98% propargyl, 97.5:2.5 e.r.

2.15 **2.18** 2 equiv. **2.20** **2.19**

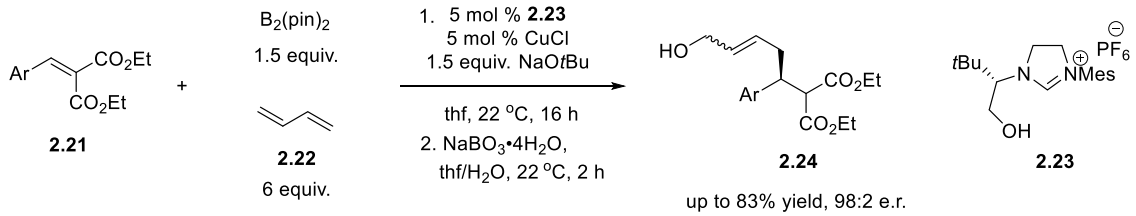
62% yield, >98% 1,6-addition, >98:2 d.r., 95:5 e.r.

Ar = 3,5-$Me_2C_6H_3$

In the same year, Hoveyda and co-workers reported multicomponent catalytic enantioselective conjugate additions of (pin)B-substituted allylcopper to α,β-unsaturated

malonate (Scheme 2.7).[13b] Desired products are obtained in up to 83% yield and 98:2 enantiomeric ratio.

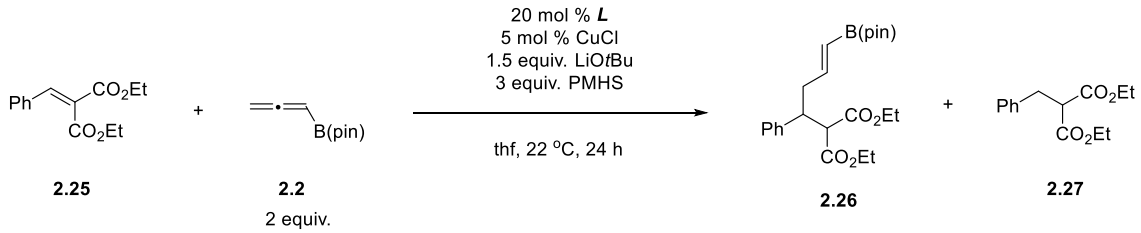
Scheme 2.7 Catalytic Enantioselective Conjugate Addition of (pin)B-Substituted Allylcopper Compounds



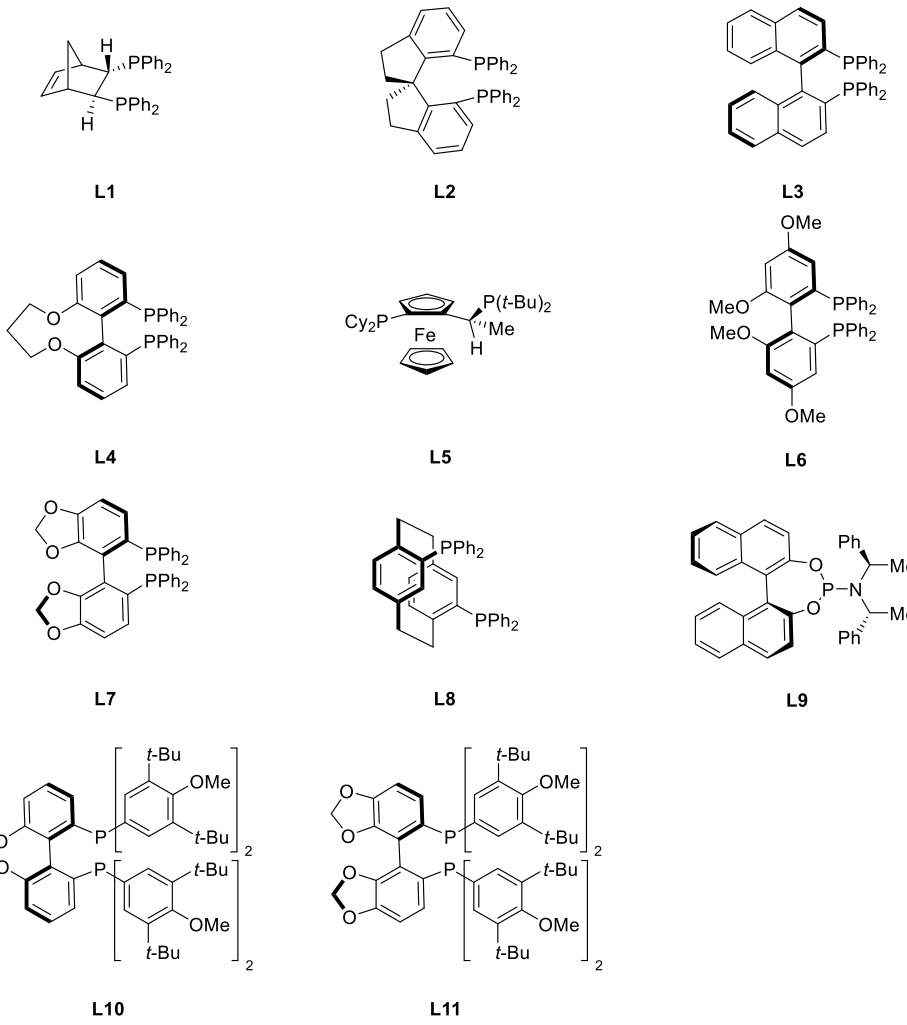
2.3 OPTIMIZATION OF REACTION CONDITIONS FOR CATALYTIC ENANTIOSELECTIVE MULTICOMPONENT ALLYL CONJUGATE ADDITION

We started our investigation with ligand screening for the multicomponent allyl conjugate addition. A variety of ligands were tested, as shown in table 2.1. One major byproduct is malonate **2.27** derived from direct reduction of α,β-unsaturated malonate **2.25**. Reactions catalyzed by some bisphosphine ligands, such as **L3**, **L4**, **L6**, **L7**, **L10** and **L11**, can generate product efficiently with moderate chemoselectivity and enantiomeric ratio. Among them, **L11** (*R*)-DTBM-SEGPHOS provided desired product **2.26** in 60% yield, 82:18 e.r. with 8:1 ratio of **2.26**/**2.27** (entry 11). A lower catalyst loading (with 6 mol % of **L11** and 5 mol % of CuCl) gave a similar result (entry 13).

Table 2.1 Ligand Screening for Cu-H Addition to Allenyl-B(pin)/Conjugate Addition



2.25 **2.2** 2 equiv. **2.26** **2.27**



L1 **L2** **L3** **L4** **L5** **L6** **L7** **L8** **L9** **L10** **L11**

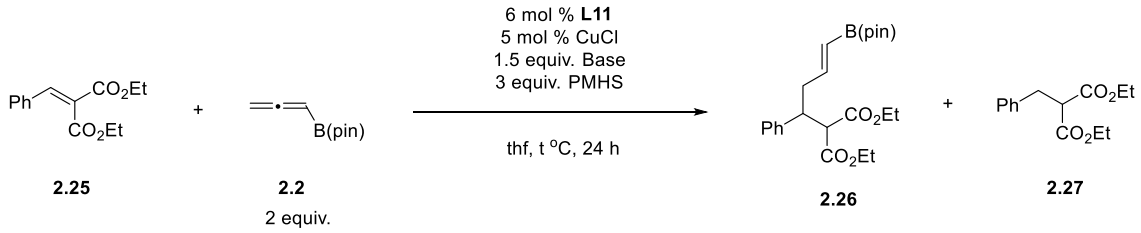
Entry	Ligand	Conv. %[b]	**2.26**:**2.27**[c]	Yield %[d]	e.r.[e]
1	**L1**	>98	NA	<2	NA
2	**L2**	>98	NA	<2	NA
3	**L3**	>98	4:1	52	55:45
4	**L4**	>98	4:1	50	67:33
5	**L5**	>98	1:1.5	21	50:50

6	**L6**	>98	6:1	58	61:39
7	**L7**	>98	6:1	68	65:35
8	**L8**	>98	NA	<2	NA
9	**L9**[f]	>98	NA	<2	NA
10	**L10**	>98	2:1	38	74:26
11	**L11**	>98	8:1	60	82:18
12	**SIMes**	>98	1:1.5	29	NA
13[g]	**L11**	>98	6:1	66	80:20
14	**-**	>98	<2:>98	NA	NA

[a] Reactions were performed under N_2 atmosphere. [b,c] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [d] Isolated yield of pure product. [e] Determined by HPLC analysis. [f] With 10 mol % of **L9** and CuCl. [g] With 6 mol % of **L11** and 5 mol % CuCl.

With **L11** in hand, we tried to further optimize the reaction conditions. A variety of conditions were tested, as shown in table 2.2. A screening of bases (entry 1-7) indicate that NaOPh (entry 5) can give the best result (compared with LiOMe, Li*O*tBu, NaOMe, Na*O*tBu, NaOAc and K*O*tBu) with 66% yield and 87:13 e.r. Reactions performed at lower temperatures are less efficient (entries 8,9 vs. 5) with lower conversion and yield, but with higher e.r. and chemoselectivity. The yield of **2.26** is further improved with a higher catalyst loading (9 mol % of **L11** and 7. 5 mol % of CuCl vs of 6 mol % of **L11** and 5 mol % of CuCl) and more reagent **2.2** (3 equiv. vs. 2 equiv.), to deliver an efficient reaction with 98% conversion of starting material **2.25**, 77% yield of conjugate addition product **2.26**, 95:5 e.r. and >20:1 ratio of **2.26**/**2.27** (entry 11).

Table 2.2 Optimization of Reaction Conditions for Cu-H Addition to Allenyl-B(pin)/Conjugate Addition



Entry	Base	Conv. %[b]	Temp.°C	**2.26**:**2.27**[c]	Yield %[d]	e.r.[e]
1	LiOMe	90	22	8:1	52	80:20
2	LiO*t*Bu	>98	22	6:1	66	80:20
3	NaOMe	>98	22	NA	<2	NA
4	NaO*t*Bu	>98	22	NA	<2	NA
5	NaOPh	>98	22	7:1	66	87:13
6	NaOAc	<5	22	NA	ND	NA
7	KO*t*Bu	>98	22	6:1	<2	65:35
8	NaOPh	82	4	>10:1	58	90:10
9	NaOPh	59	-30	>20:1	42	94:6
10[f]	NaOPh	86	-30	>20:1	71	95:5
11[f,g]	NaOPh	98	-30	>20:1	77	95:5

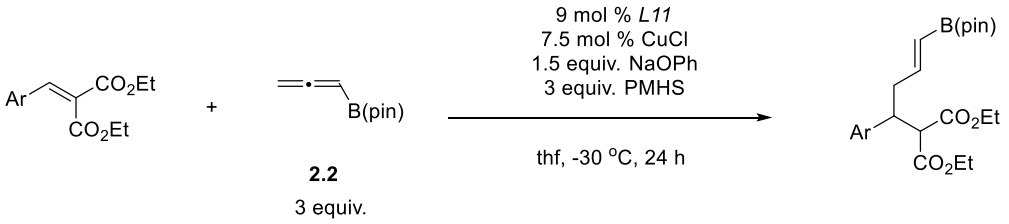
[a] Reactions were performed under N_2 atmosphere. [b,c] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [d] Isolated yield of pure product. [e] Determined by HPLC analysis. [f] With 9 mol % of **L11** and 7.5 mol % CuCl. [g] With 3 equiv. of **2.2**.

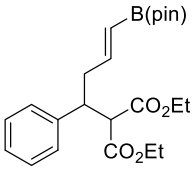
2.4 SCOPE OF CATALYTIC ENANTIOSELECTIVE MULTICOMPONENT ALLYL CONJUGATE ADDITION

With the optimum conditions in hand, we examined the substrate scope for the multicomponent allyl conjugate addition. As shown in scheme 2.8, halogen substituents (**2.26c-d**) are well tolerated. Sterically demanding substrate **2.26b**, although less efficient,

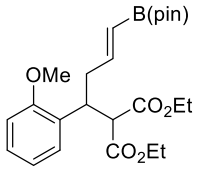
works well (67% yield and 92:8 e.r.). Electron deficient **2.26f** and rich (**2.26e**) substrates are suitable. Heterocycle containing substrates (**2.26h-i**) are also compatible with reaction conditions to deliver products in high efficiency (84% yield, 95:5 e.r.; 75% yield, 92:8 e.r., respectively). Cu-H addition products, as well as *Z*- products are not observed in any of these cases.

Scheme 2.8 Substrate Scope for Cu-H Addition to Allenyl-B(pin)/Conjugate Addition

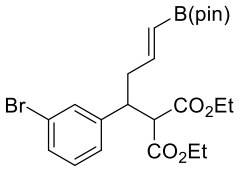




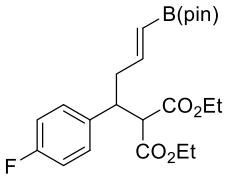
2.26
98% conv., 77% yield,
95:5 e.r.



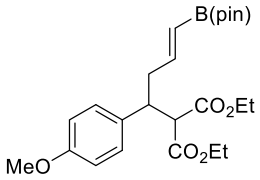
2.26b
84% conv., 67% yield,
92:8 e.r.



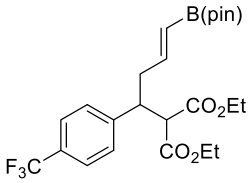
2.26c
90% conv., 66% yield,
91:9 e.r.



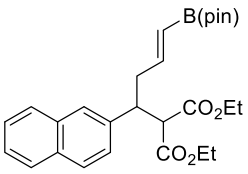
2.26d
>98% conv., 73% yield,
94:6 e.r.



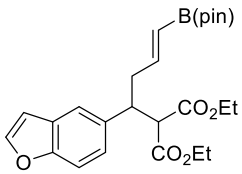
2.26e
>98% conv., 82% yield,
96:4 e.r.



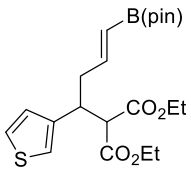
2.26f
90% conv., 65% yield,
91:9 e.r.



2.26g
91% conv., 55% yield,
95:5 e.r.



2.26h
>98% conv., 84% yield,
95:5 e.r.

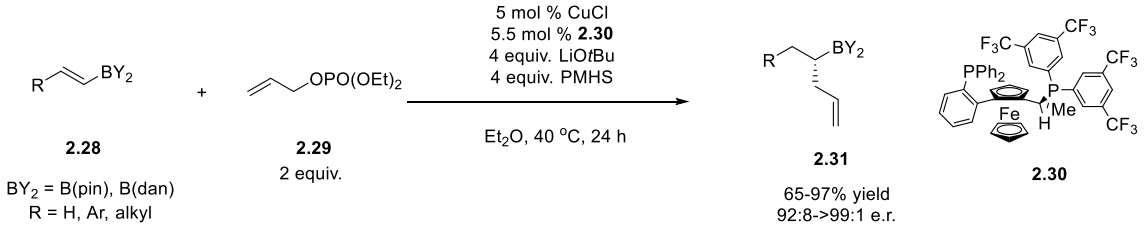


2.26i
91% conv., 75% yield,
92:8 e.r.

2.5 FUNCTIONALIZATION OF PRODUCTS OF CATALYTIC ENANTIOSELECTIVE MULTICOMPONENT ALLYL CONJUGATE ADDITION

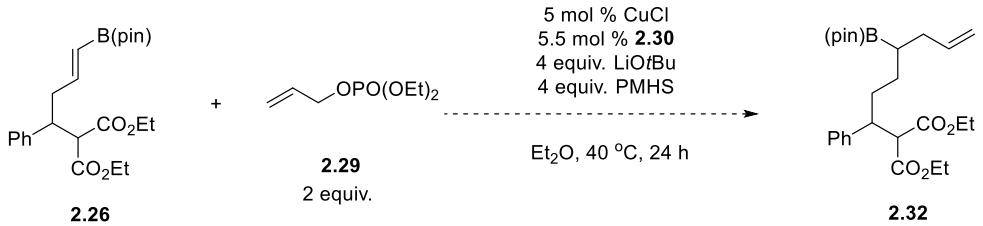
Alkenyl boronic esters are broadly useful functional motifs in organic synthesis.[18] Not only they possess high chemical stability, they can also participate in a variety of transformations. In 2017, Yun and co-workers reported a Cu-catalyzed regio- and enantioselective hydroallylation of alkenyl boronates and boramides (scheme 2.9).[19]

Scheme 2.9 Cu-Catalyzed Enantioselective Hydroallylation of Alkenyl-B(pin)



We tested the Cu-catalyzed enantioselective hydroallylation of alkenyl boronates as reported above (scheme 2.10). Under the reported conditions, we observed low conversion of alkenyl-B(pin) **2.26** (30~40%), and recovered non-separable mixture.

Scheme 2.10 Fuctionalization of Alkenyl-B(pin)



(18) (a) Ramachandran, P. V.; Brown, H. C. Recent Advances in Borane Chemistry. In *Organoboranes for Synthesis*; ACS Symposium Series 783; American Chemical Society: Washington, DC, 2001. (b) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (c) Brown, H. C.; Campbell, J. B., Jr. *Aldrichimica Acta* **1981**, *14*, 3. (d) Hall, D. G., Ed. *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine,* 2nd ed.; Wiley-VCH: Weinheim, 2011.
(19) J. T. Han, W. J. Jang, N. Kim, J. Yun, *J. Am. Chem. Soc.* **2016**, *138*, 15146−15149.

2.6 CONCLUSION

In this chapter, we have developed a facile multicomponent catalytic process that begins with a chemo- and siteselective copper–hydride addition to allenyl-B(pin) followed by enantioselective conjugate addition of the resulting allylcopper intermediate to α,β-unsaturated malonates, generating products that contain a stereogenic center and an easily functionalizable alkenyl-B(pin) in up to 84% yield, >98:2 E/Z selectivity and 96:4 enantiomeric ratio. The transformations are catalyzed by chiral Cu complexes derived from commercially available bisphosphines. Further studies on expanding substrate scope, functionalization of products and application towards synthesis of valuable compounds are ongoing.

2.7 EXPERIMENTAL

General

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, νmax in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet, app. = apparent), and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz)

spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm). High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralpak AZ–H (5.0 × 250 mm), Chiralpak OD–H (5.0 × 250 mm)) in comparison with authentic racemic materials. Specific rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich Chemical Co.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific) in air.

Reagents and Ligands

Allenylboronic acid pinacol ester (2.2): purchased from Aldrich Chemical Co. and used as received.

Copper (I) chloride: purchased from Strem Chemicals Inc. and used as received.

Diethyl allyl phosphate (2.29): purchased from Aldrich Chemical Co. and used as received.

Diethyl benzylidenemalonate (2.25): purchased from Aldrich Chemical Co. and used as received.

Enoate (2.25b-i): prepared according to previously reported procedures.[20]

L1-L11: purchased from Strem Chemicals Inc. and used as received.

Lithuim *tert*-butoxide: purchased from Strem Chemicals Inc. and used as received.

Lithuim methoxide: purchased from Strem Chemicals Inc. and used as received.

Poly(methylhydrosiloxane): purchased from Aldrich Chemical Co. and used as received.

Potassium *tert*-butoxide: purchased from Strem Chemicals Inc. and used as received.

SIMes chloride: purchased from Aldrich Chemical Co. and used as received.

Sodium *tert*-butoxide: purchased from Strem Chemicals Inc. and used as received.

Sodium methoxide: purchased from Strem Chemicals Inc. and used as received.

Sodium phenoxide: purchased from Strem Chemicals Inc. and used as received.

Representative Procedure for Multicomponent Allyl Conjugate Addition:

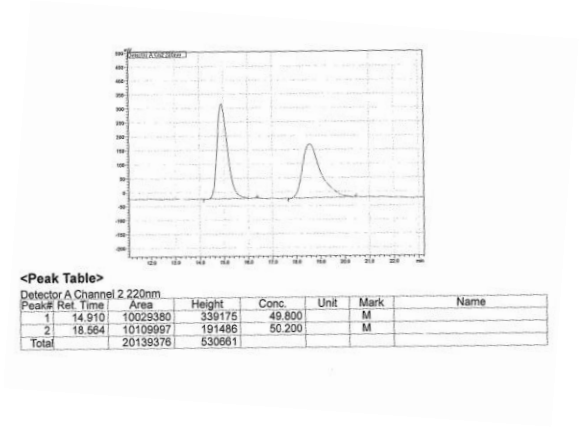
An oven-dried 1 dram vial equipped with a stir bar was weighed and charged with phosphine **L11** (10.6 mg, 9 μmol), CuCl (0.75 mg, 7.5 μmol) and NaOPh (14.4 mg, 150 μmol) in a N_2-filled glove box. Freshly distilled THF (1.0 mL) was added to the vial and the mixture was allowed to stir at 22 °C for 0.5 h. After that, PMHS (18.0 mg, 0.3 mmol) and allenyl-B(pin) **2.2** (49.8 mg, 0.3 mmol) was added into the vial. The vial was sealed with a cap (phenolic open top cap with a red PFTE/white silicon septum) and electrical tape, removed from the glove box, and cooled down to -78 ºC before malonate (24.8 mg,

(20) C. F. H. Allen, F. W. Spangler, *Org. Syn.* **1945**, *25*, 42.

0.10 mmol) was added by a syringe. The vial was then moved into the cryocool and kept at -30 ºC for 24 h. After that, the mixture was passed through a short plug of silica gel and eluted with Et_2O. The organic layer was concentrated *in vacuo* and purified by silica gel chromatography to afford the desired product as solorless oil.

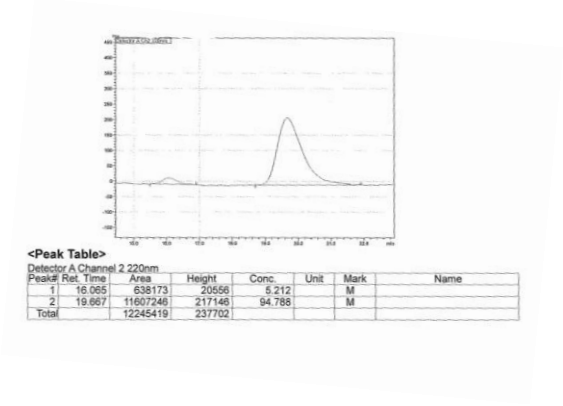
Diethyl (*E*)-2-(1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26):

IR (neat): 2979 (m), 1732 (s), 1638 (m), 1365 (s), 1321 (m), 1250 (m), 1144 (s), 850 (w), 701 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.15 (5H, m), 6.37 (1H, dt, *J* = 17.6, 6.8 Hz), 5.34 (1H, dd, *J* = 18.0, 1.6 Hz), 4.19 (2H, q, *J* = 7.2 Hz), 3.88 (2H, q, *J* = 7.2 Hz), 3.66 (1H, d, *J* = 10.4 Hz), 3.57-3.51 (1H, m), 2.59-2.55 (1H, m), 1.26 (3H, t, *J* = 7.2 Hz), 1.20 (12H, s), 0.95 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 167.7, 150.2, 140.4, 128.3, 128.2, 126.9, 83.0, 61.5, 61.1, 58.0, 44.7, 40.4, 24.7, 24.7, 14.0, 13.7; HRMS (ESI^+): Calcd for $C_{23}H_{34}BO_6$ $[M+H]^+$: 417.2448; Found: 417.2455. Specific rotation: $[\alpha]_D^{20}$ 17.3 (c 1.5, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.910	10029380	339175	49.800		M	
2	18.564	10109997	191486	50.200		M	
Total		20139376	530661				



<Peak Table>
Detector A Channel 2 220nm

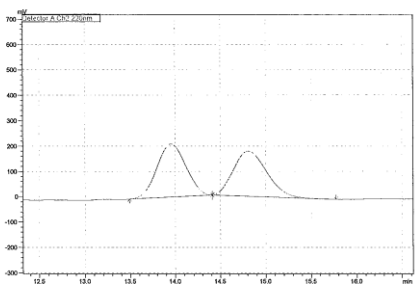
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	16.065	638173	20556	5.212		M	
2	19.667	11607246	217146	94.788		M	
Total		12245419	237702				

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	14.910	49.800	1	16.065	5.212
2	18.564	50.200	2	19.667	94.788

Diethyl (*E*)-2-(1-(2-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26b):

IR (neat): 2979 (m), 1732 (s), 1637 (m), 1493 (m), 1365 (s), 1320 (m), 1244 (s), 1144 (s), 1030 (m), 849 (w), 754 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.02 (2H, m), 6.85-6.81 (2H, m), 6.41 (1H, dt, J = 10.8, 6.8 Hz), 5.31 (1H, d, J = 18.0 Hz), 4.18 (2H, q, J = 7.2 Hz), 3.99 (1H, d, J = 14.4 Hz), 3.94-3.82 (6H, m), 2.73-2.66 (1H, m), 2.57-2.51 (1H, m), 1.27 (3H, t, J = 7.2 Hz), 1.20 (12H, s), 0.96 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 168.2, 157.6, 151.4, 129.8, 128.3, 127.9, 120.2, 110.7, 82.9, 61.3, 60.9, 55.8, 55.2, 38.5, 24.7, 14.1, 13.7; HRMS (ESI^+): Calcd for $C_{24}H_{36}BO_7$ $[M+H]^+$: 447.2554; Found: 447.255. Specific rotation: $[\alpha]_D^{20}$ −4.9 (c 1.5, $CHCl_3$) for an enantiomerically enriched sample of 92:8 e.r.

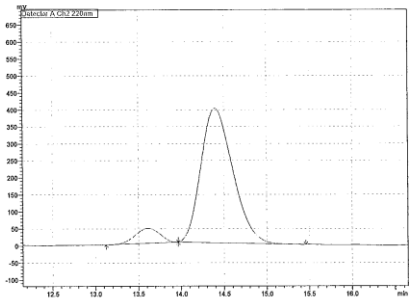
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	13.954	4676515	209464	50.660		M
2	14.810	4554717	178229	49.340		M
Total		9231232	387693			



<Peak Table>

Detector A Channel 2 220nm

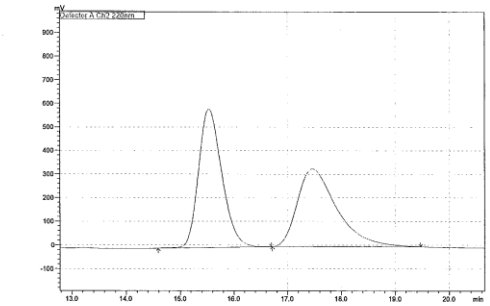
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	13.612	863766	43755	7.826		M
2	14.398	10173910	395196	92.174		M
Total		11037676	438950			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	13.954	50.660	1	13.612	7.826
2	14.810	49.340	2	14.398	92.174

Diethyl (*E*)-2-(1-(3-bromophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26c):

IR (neat): 2979 (m), 1732 (s), 1638 (m), 1365 (s), 1322 (m), 1249 (m), 1144 (s), 849 (w), 697 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.31 (2H, m), 7.15-7.13 (2H, m), 6.34 (1H, dt, *J* = 18.0, 7.2 Hz), 5.35 (1H, d, *J* = 17.6 Hz), 4.23-4.18 (2H, m), 3.93 (2H, q, *J* = 7.2 Hz), 3.63 (1H, d, *J* = 10.4 Hz), 3.54-3.48 (1H, m), 2.59-2.49 (2H, m), 1.28 (3H, t, *J* = 7.2 Hz), 1.20 (12H, s), 1.00 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 167.4,149.5, 142.8, 131.4, 130.1, 129.8, 127.0, 122.3, 83.1, 61.6, 61.3, 57.7, 44.3, 40.1, 24.7, 14.0, 13.7; HRMS (ESI^+): Calcd for $C_{23}H_{33}BBrO_6$ $[M+H]^+$: 495.1554; Found: 495.1567. Specific rotation: $[\alpha]_D^{20}$ 1.4 (c 2.0, $CHCl_3$) for an enantiomerically enriched sample of 91:9 e.r.

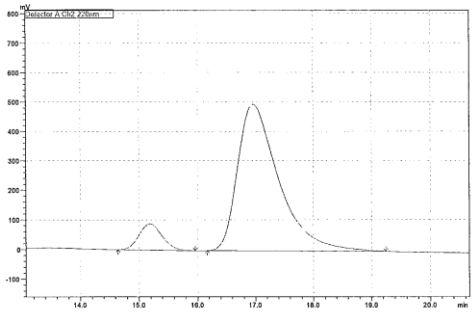
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	15.535	17633935	586052	51.317		M
2	17.464	16728949	328411	48.683		M
Total		34362884	914464			



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Detector A Channel 2 220nm

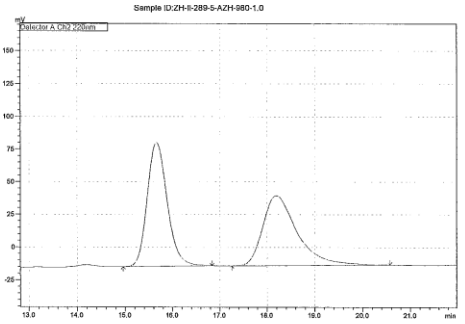
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	15.183	2412825	87568	8.976		M
2	16.961	24468258	496443	91.024		M
Total		26881083	584011			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	15.535	51.317	1	15.183	8.976
2	17.464	48.683	2	16.961	91.024

Diethyl (*E*)-2-(1-(4-fluorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26d):

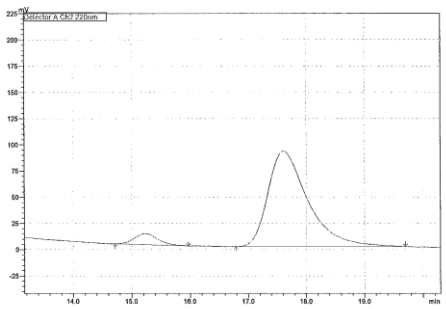
IR (neat): 2980 (m), 1731 (s), 1638 (m), 1510 (m), 1364 (s), 1320 (s), 1225 (s), 1143 (s), 1033 (m), 839 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.13 (2H, m), 6.98-6.92 (2H, m), 6.34 (1H, dt, J = 18.0, 7.2 Hz), 5.34 (1H, d, J = 18.0 Hz), 4.20 (2H, q, J = 7.2 Hz), 3.93-3.88 (2H, m), 3.62 (1H, d, J = 12.4 Hz), 3.56-3.50 (1H, m), 2.61-2.46 (2H, m), 1.27 (3H, t, J = 7.2 Hz), 1.21 (12H, s), 1.00 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.0, 167.6, 161.7 (d, J = 244 Hz), 149.8, 136.0 (d, J = 3 Hz), 129.8 (d, J = 8 Hz), 115.1 (d, J = 21 Hz), 83.0, 61.6, 61.2, 58.0, 43.9, 40.4, 24.7, 14.0, 13.7; HRMS (ESI^+): Calcd for $C_{23}H_{33}BFO_6$ $[M+H]^+$: 435.2354; Found: 435.2347.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	15.659	2774854	94842	50.945		M
2	18.193	2671887	53419	49.055		M
Total		5446741	148262			



<Peak Table>
Detector A Channel 2 220nm

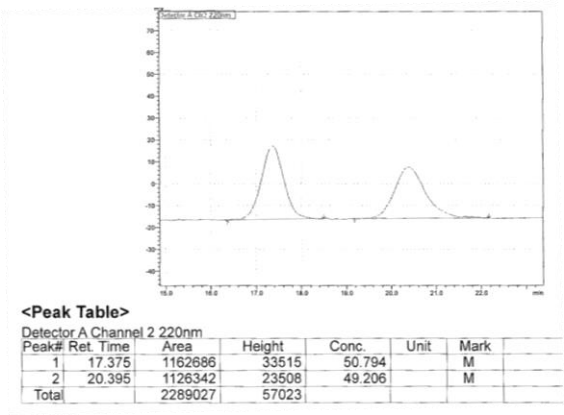
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	15.220	293259	10400	6.309		M
2	17.610	4355134	91027	93.691		M
Total		4648393	101427			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	15.659	50.945	1	15.220	6.309
2	18.193	49.055	2	17.610	93.691

Diethyl (*E*)-2-(1-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26e):

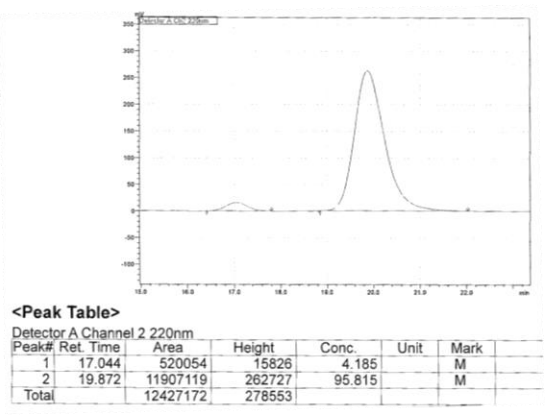
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.10 (2H, m), 6.81-6.78 (2H, m), 6.37 (1H, dt, *J* = 18.0, 6.8 Hz), 5.35 (1H, d, *J* = 18.0 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 3.90 (2H, q, *J* = 7.2 Hz), 3.76 (3H, s), 3.61 (1H, d, *J* = 10.4 Hz), 3.52-3.46 (1H, m), 2.55-2.51 (2H, m), 1.27 (3H, t, *J* = 7.6 Hz), 1.20 (12H, s), 0.98 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 167.7, 158.4, 150.4, 132.4, 129.3, 113.6, 83.0, 61.4, 61.1, 58.2, 55.1, 43.9, 40.5, 24.7, 14.1, 13.8.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 94.0:6.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	17.375	1162686	33515	50.794		M
2	20.395	1126342	23508	49.206		M
Total		2289027	57023			



<Peak Table>
Detector A Channel 2 220nm

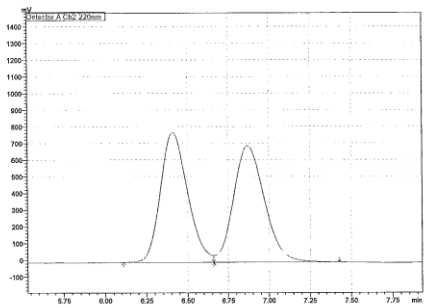
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	17.044	520054	15826	4.185		M
2	19.872	11907119	262727	95.815		M
Total		12427172	278553			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	17.375	50.794	1	17.044	4.185
2	20.395	49.206	2	19.872	95.815

Diethyl (*E*)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)malonate (2.26f):

IR (neat): 2980 (w), 1733 (m), 1638 (w), 1364 (m), 1324 (s), 1143 (s), 1069 (s), 848 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (2H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz), 6.31 (1H, dt, J = 18.0, 6.8 Hz), 5.35 (1H, d, J = 17.6 Hz), 4.24-4.19 (2H, m), 3.93-3.87 (2H, m), 3.69-3.59 (2H, m), 2.63-2.52 (2H, m), 1.30-1.23 (3H, m), 1.21 (12H, s), 0.96 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 167.4, 149.2, 144.6, 129.1 (q, J = 29 Hz), 128.7, 125.5-125.2 (m), 122.8, 83.1, 61.7, 61.3, 57.5, 40.0, 24.7, 24.7, 14.0, 13.6.

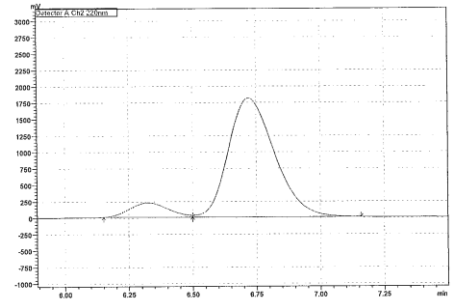
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	6.411	9024297	779118	49.635		M
2	6.870	9157073	697917	50.365		V M
Total		18181370	1477035			



<Peak Table>

Detector A Channel 2 220nm

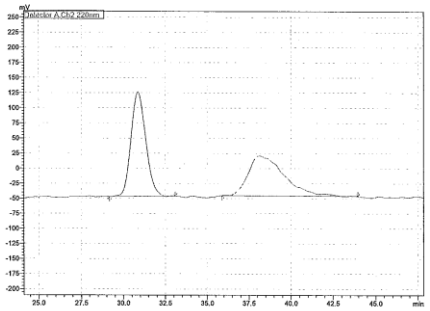
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	6.324	2311459	220882	9.257		M
2	6.720	22659361	1805236	90.743		V M
Total		24970819	2026118			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	6.411	49.635	1	6.324	9.257
2	6.870	50.365	2	6.720	90.743

Diethyl (*E*)-2-(1-(naphthalen-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26g):

IR (neat): 2978 (m), 1731 (s), 1637 (m), 1362 (s), 1320 (s), 1143 (s), 1031 (m), 849 (m), 748 (m), 479 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.75 (3H, m), 7.65 (1H, s), 7.45-7.40 (2H, m), 7.37-7.34 (1H, m), 6.40 (1H, dt, J = 17.6, 6.8 Hz), 5.38 (1H, d, J = 18.0 Hz), 4.23 (2H, q, J = 7.2 Hz), 3.88-3.70 (4H, m), 2.69-2.66 (2H, m), 1.30-1.26 (3H, m), 1.18 (12H, s), 0.86 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 167.7, 150.1, 137.9, 133.3, 132.6, 128.0, 127.8, 127.5, 127.3, 126.3, 125.9, 125.6, 83.0, 61.6, 61.2, 58.1, 44.8, 40.3, 24.7, 14.1, 13.6.

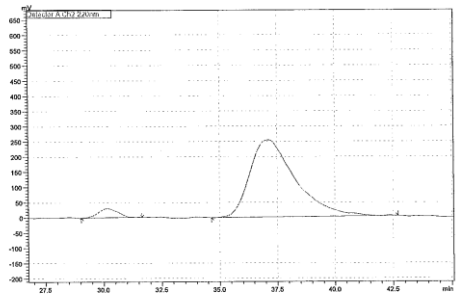
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	30.861	10662153	172976	51.851		M
2	38.114	9900994	66014	48.149		M
Total		20563147	238990			



<Peak Table>

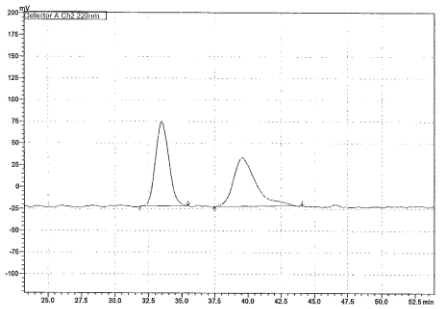
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	30.148	1757721	29846	4.822		M
2	37.127	34696202	253425	95.178		M
Total		36453924	283271			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	30.861	51.851	1	30.148	4.822
2	38.114	48.149	2	37.127	95.178

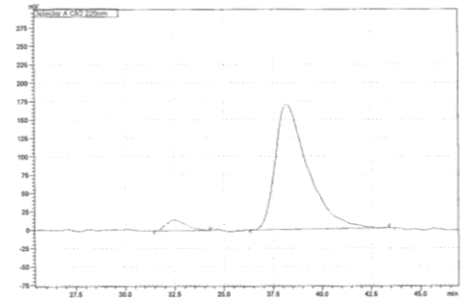
Diethyl (*E*)-2-(1-(benzofuran-5-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)malonate (2.26h):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (1H, d, J = 0.4 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.39 (1H, d, J = 8.4 Hz), 7.13 (1H, dd, J = 8.8, 1.6 Hz), 6.70 (1H, dd, J = 2.4, 0.8 Hz), 6.38 (1H, dt, J = 18.0, 6.8 Hz), 5.36 (1H, d, J = 18.0 Hz), 4.21 (2H, q, J = 6.8 Hz), 3.88-3.83 (2H, m), 3.71-3.61 (2H, m), 2.61-2.59 (2H, m), 1.27 (3H, t, J = 6.8 Hz), 1.19 (12H, s), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 167.7, 154.0, 150.3, 145.1, 134.9, 127.4, 124.7, 120.9, 111.0, 106.6, 83.0, 61.5, 61.1, 58.5, 44.6, 40.8, 24.7, 14.1, 13.7; HRMS (ESI^+): Calcd for $C_{25}H_{37}BO_7N$: 474.2663; Found: 474.2674. Specific rotation: $[\alpha]_D^{20}$ -8.3 (c 2.0, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	33.478	6747835	96984	50.647		M
2	39.565	6575350	55517	49.353		M
Total		13323185	152501			



<Peak Table>
Detector A Channel 2 220nm

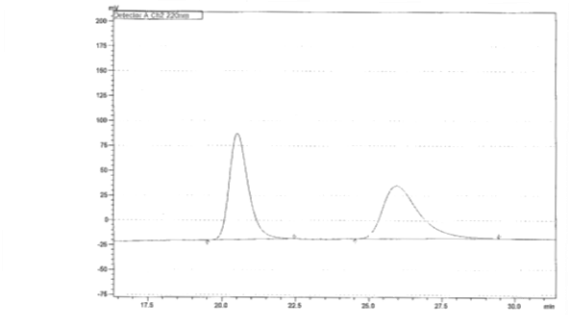
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	32.476	1028449	14548	4.977		M
2	38.203	19637120	170395	95.023		M
Total		20665569	184943			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	33.478	50.647	1	32.476	4.977
2	39.565	49.353	2	38.203	95.023

Diethyl (*E*)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-3-yl)but-3-en-1-yl)malonate (2.26i):

IR (neat): 2979 (m), 1732 (s), 1638 (m), 1363 (s), 1321 (s), 1144 (s), 849 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.18 (1H, m), 7.01-7.00 (1H, m), 6.94 (1H, d, J = 4.8 Hz), 6.40 (1H, dt, J = 18.0, 6.8 Hz), 5.37 (1H, dd, J = 18.0, 1.6 Hz), 4.17 (2H, q, J = 7.2 Hz), 3.94 (2H, q, J = 6.8 Hz), 3.72-3.66 (1H, m), 3.60 (1H, d, J = 9.6 Hz), 2.57-2.52 (2H, m), 1.25 (3H, t, J = 6.8 Hz), 1.20 (12H, s), 1.02 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 167.8, 150.2, 141.1, 127.2, 125.2, 122.1, 83.0, 61.5, 61.2, 57.7, 40.2, 39.9, 24.7, 24.7, 14.0, 13.8; HRMS (ESI^+): Calcd for $C_{21}H_{32}BO_6S$ $[M+H]^+$: 423.2013; Found: 423.2026. Specific rotation: $[\alpha]_D^{20}$ 8.3 (c 1.0, $CHCl_3$) for an enantiomerically enriched sample of 92:8 e.r.

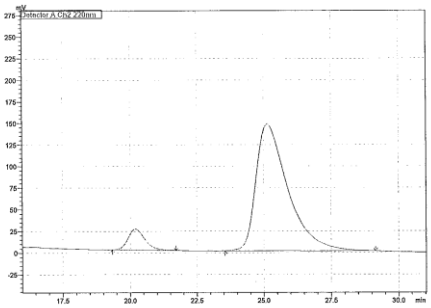
Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ–H column, 98.0:2.0 hexanes/*i*PrOH, 1.0 mL/min, 220 nm.



<Peak Table>

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	20.530	4777526	106797	50.860		M
2	25.964	4615893	53407	49.140		M
Total		9393419	160204			

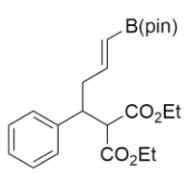


<Peak Table>

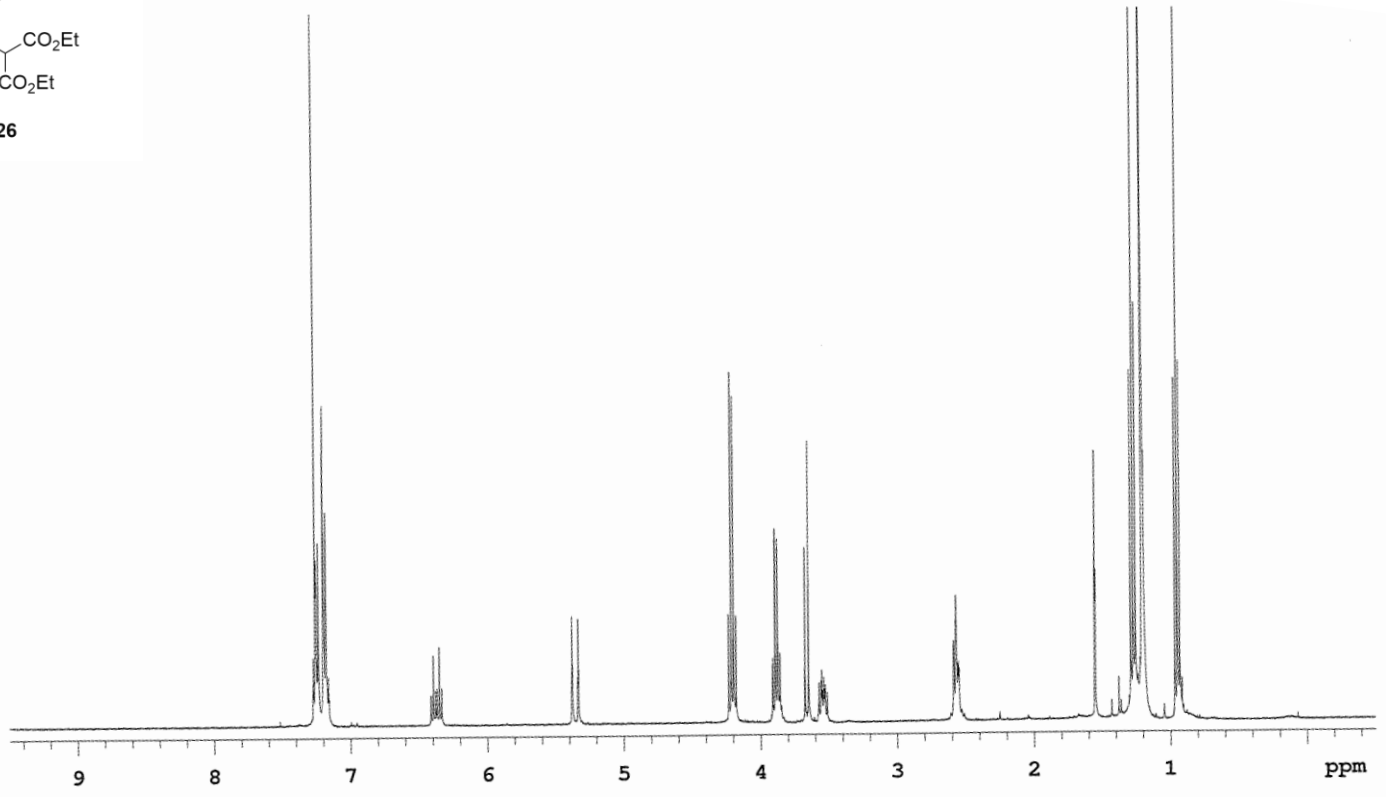
Detector A Channel 2 220nm

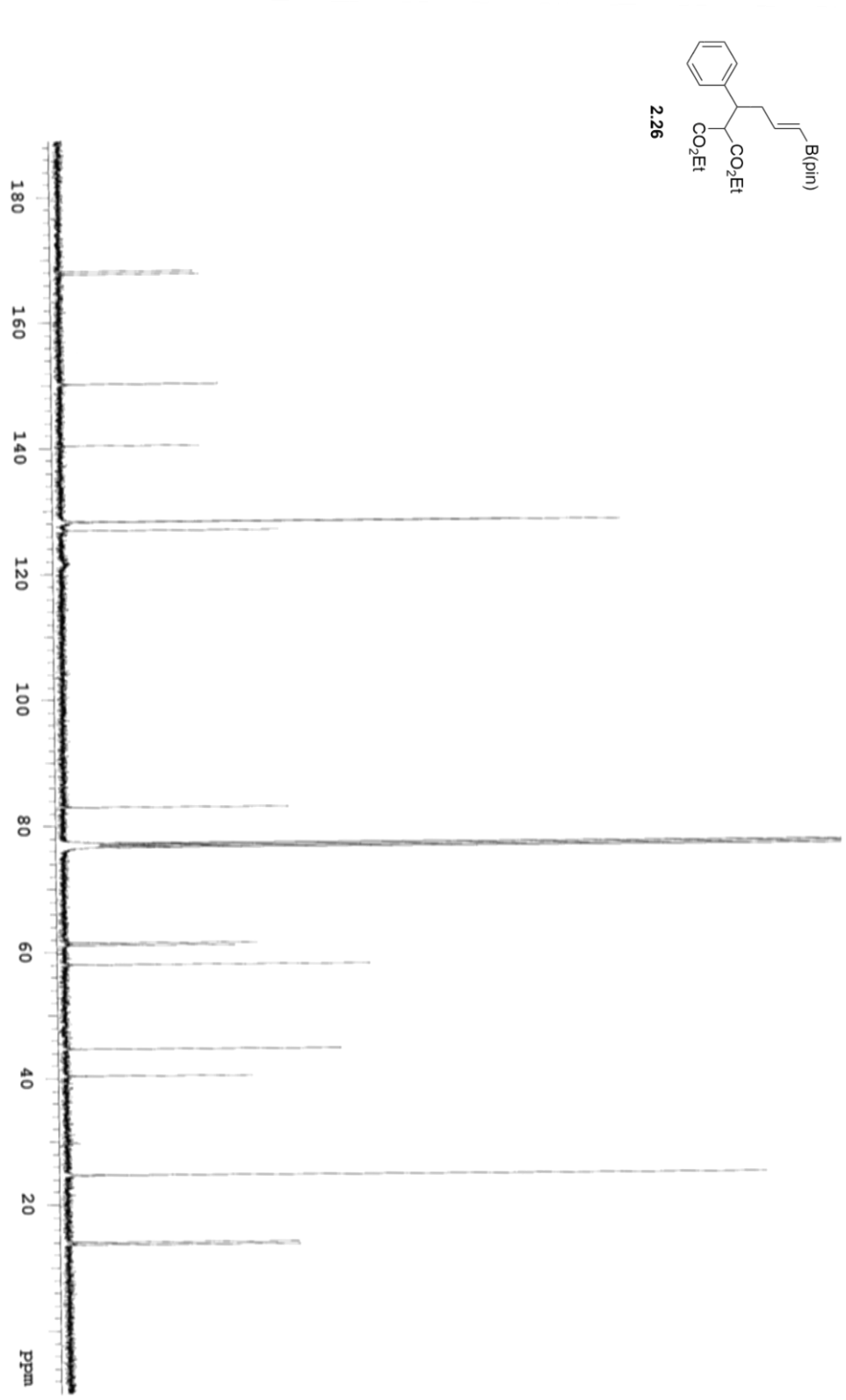
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	20.189	1054293	24057	7.996		M
2	25.140	12130352	146770	92.004		M
Total		13184645	170827			

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	20.530	50.860	1	20.189	7.996
2	25.964	49.140	2	25.140	92.004



2.26

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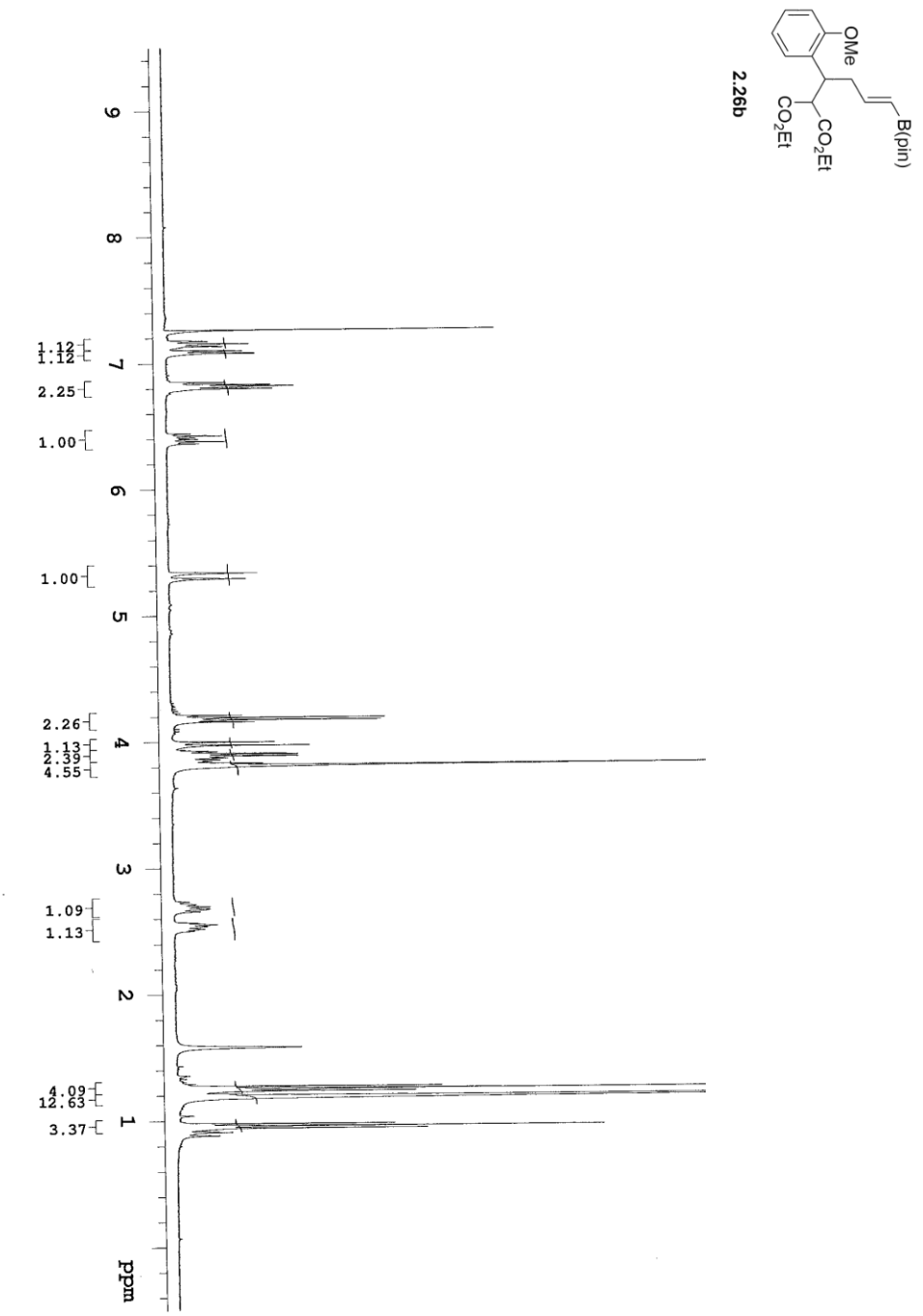
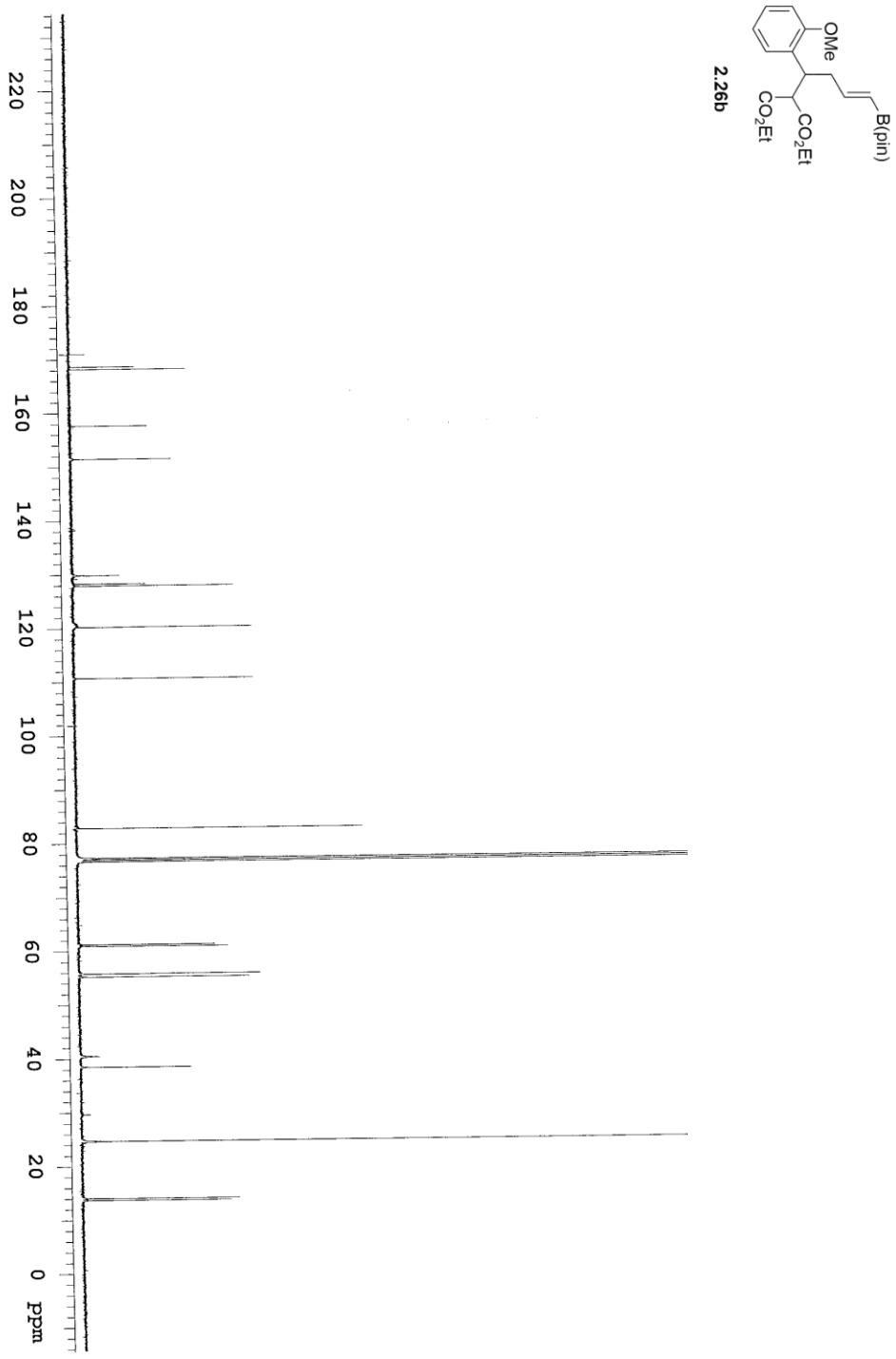
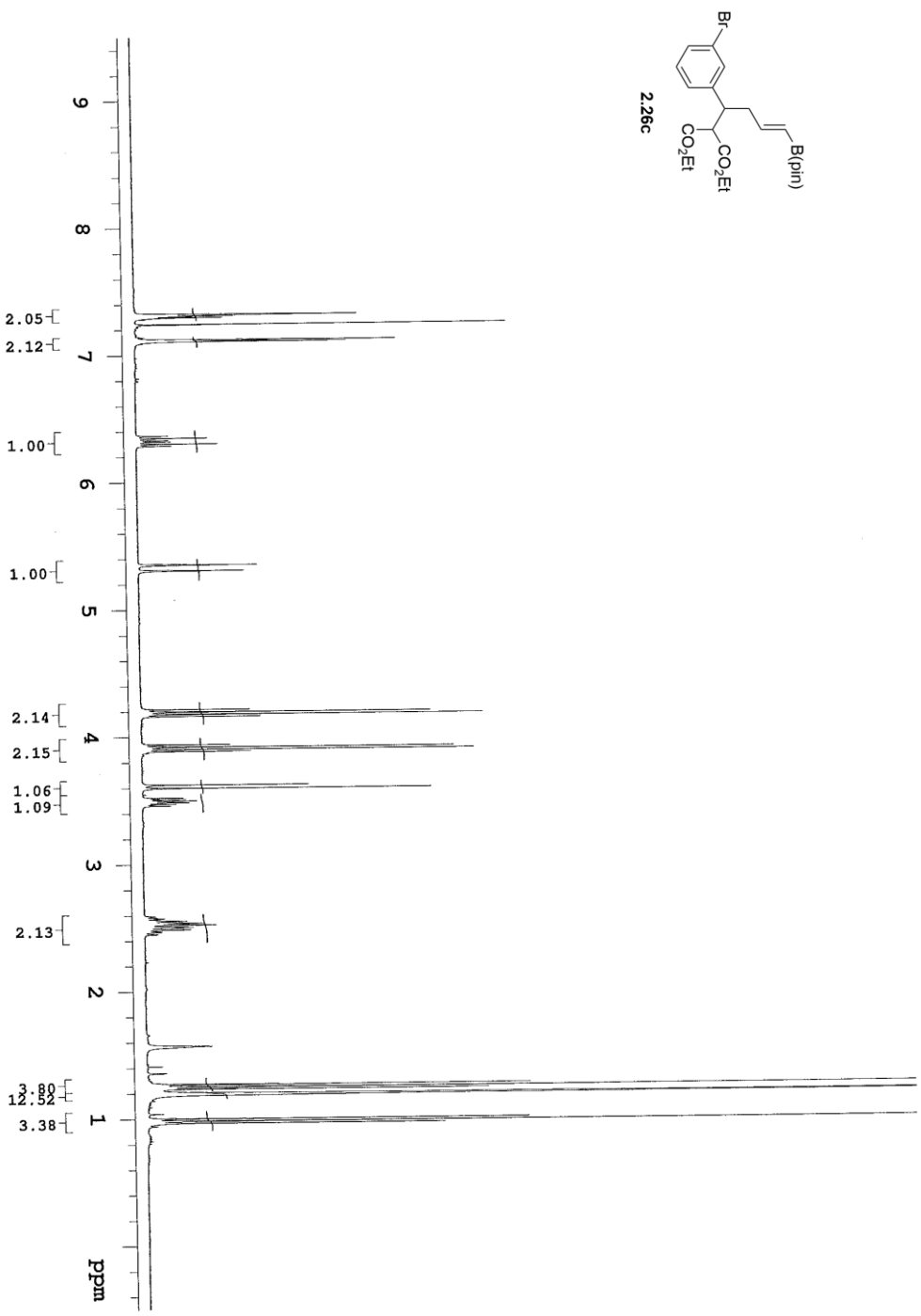
CO2Et
2.26
180
160
140
120
100
80
60
40
20
ppm


OMe
B(pin)
CO2Et
CO2Et
2.26b
1.12
1.12
2.25
1.00
1.00
2.26
1.13
2.39
4.55
1.09
1.13
4.09
12.63
3.37
ppm


OMe
B(pin)
CO2Et
CO2Et
2.26b
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Br
B(pin)
CO2Et
CO2Et
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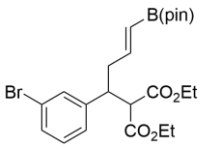
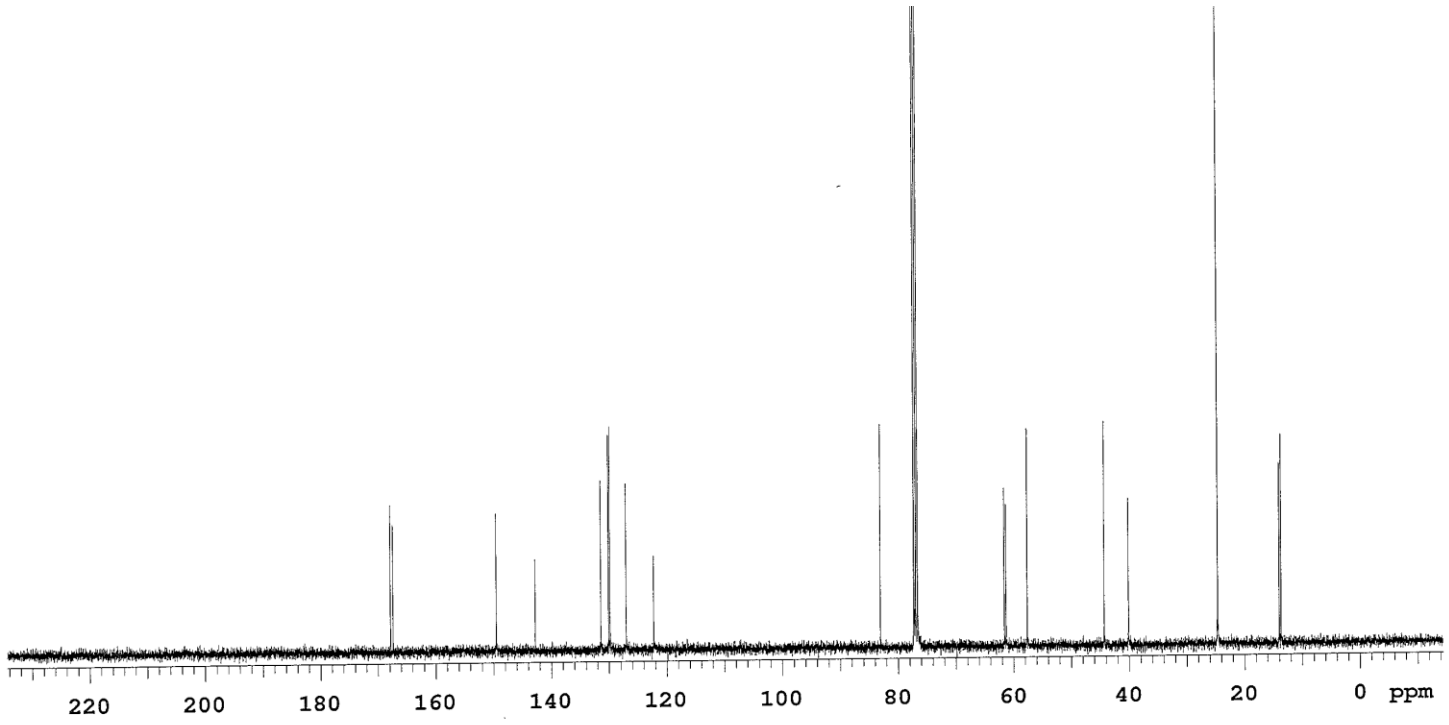
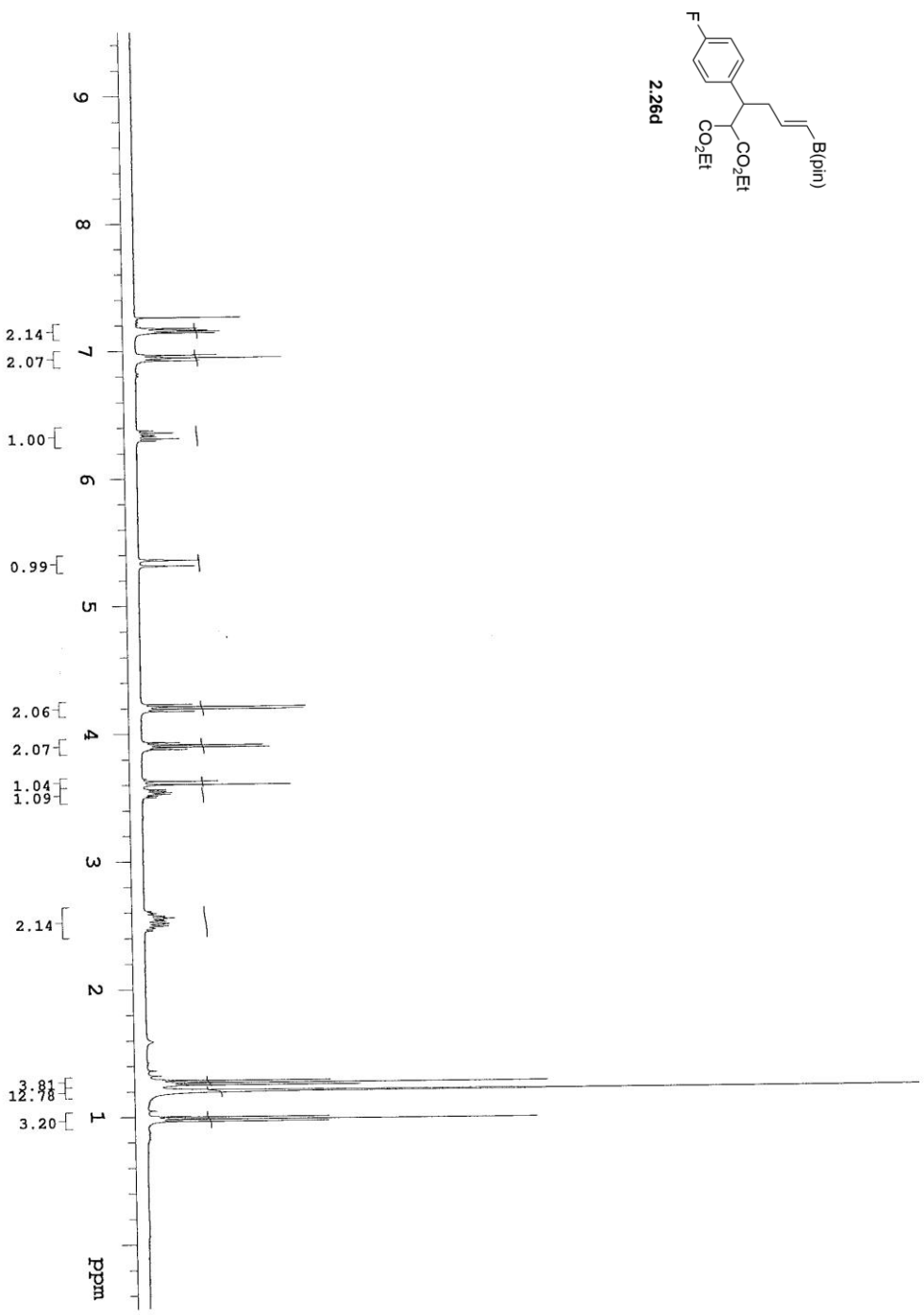
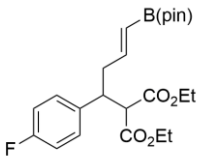
2.12
1.00
1.00
2.14
2.15
1.06
1.09
2.13
3.80
12.52
3.38
ppm



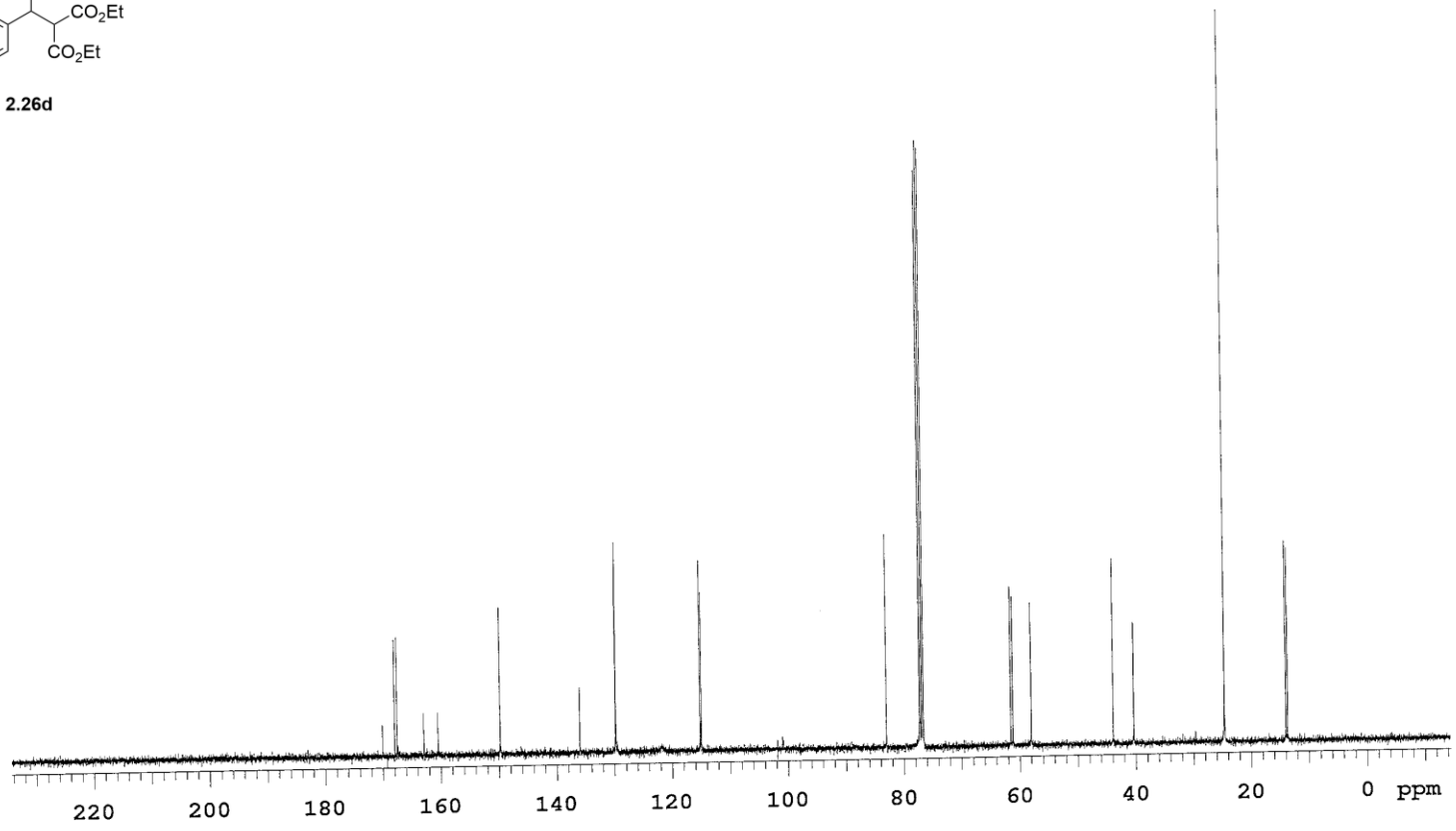
2.26c

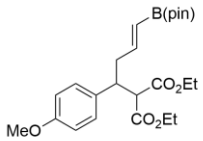



F
B(pin)
CO2Et
CO2Et
2.26d
2.14
2.07
1.00
0.99
2.06
2.07
1.04
1.09
2.14
3.81
12.78
3.20
ppm



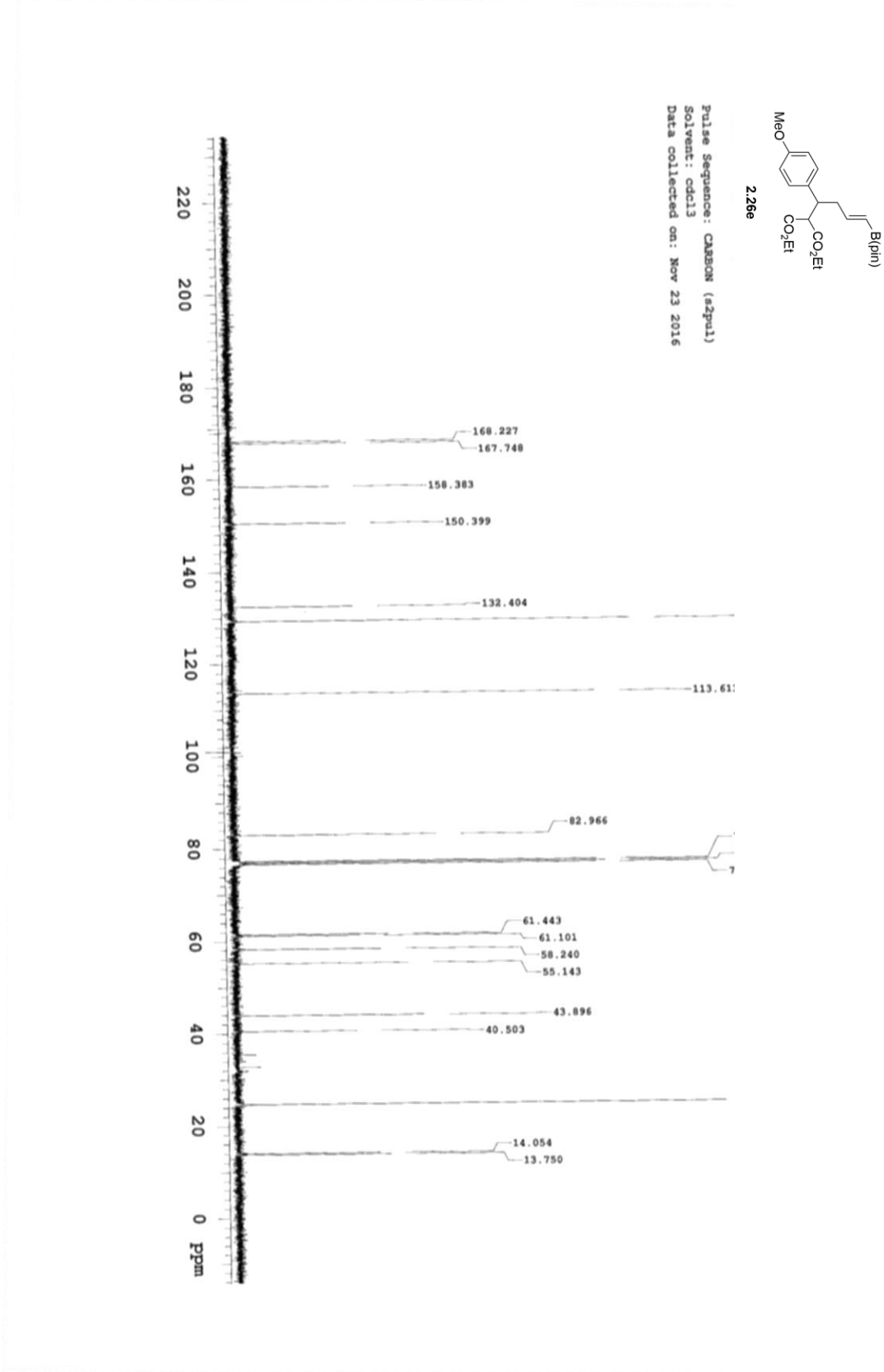
2.26d

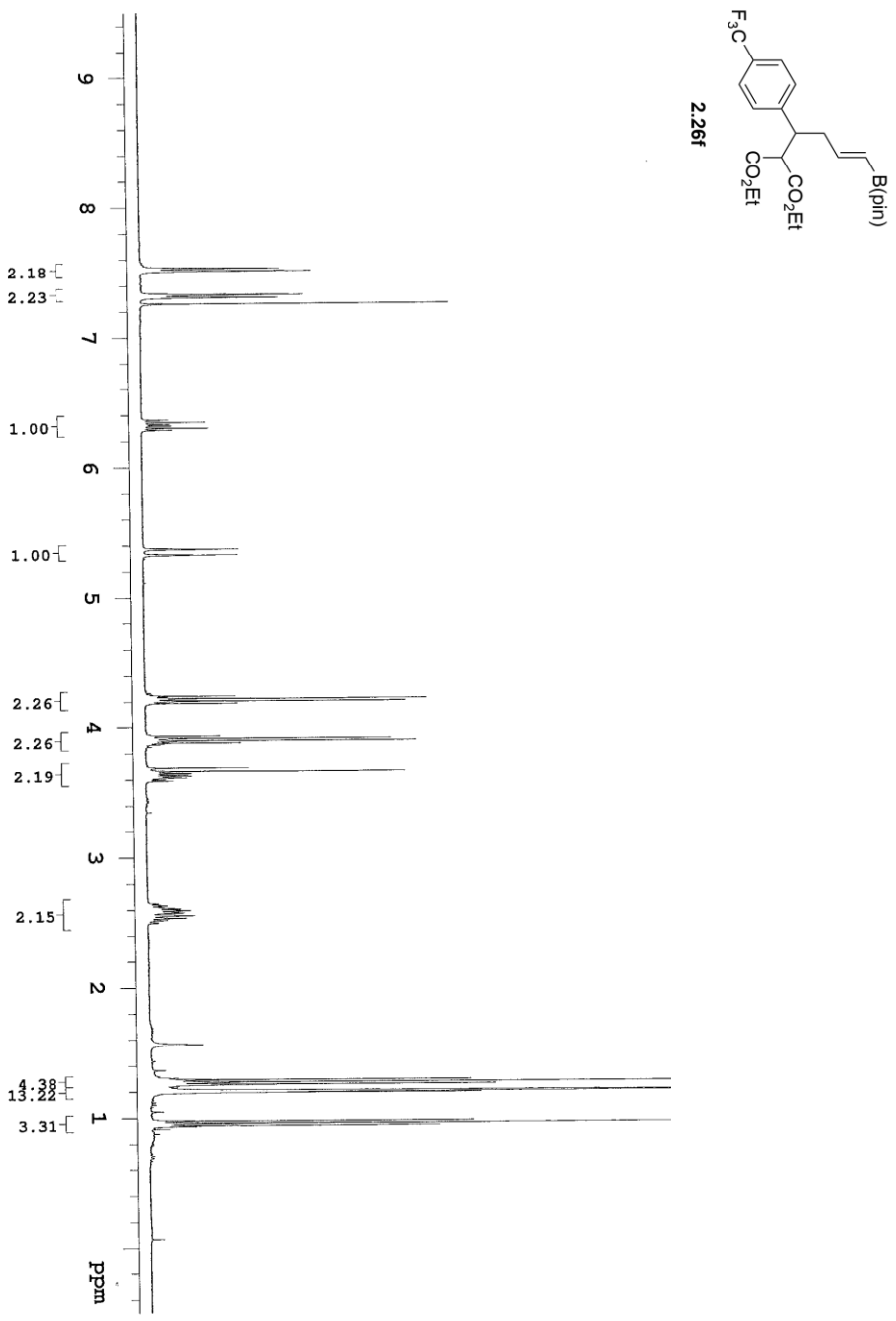


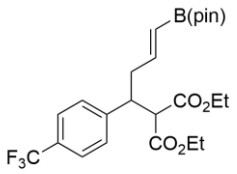

B(pin)
CO2Et
CO2Et
MeO

2.26e

Zy-3-28-3p
Sample Name Zy-3-28-3p
Date collected 2016-11-23
Pulse sequence PROTON
Solvent cdcl3
Temperature 25
Spectrometer nmr13-vnmrs400
Study owner mengf
Operator mengf
9
8
7
6
5
4
3
2
1
ppm
2.07
2.05
1.00
0.99
2.04
2.06
3.08
1.07
1.07
2.08
3.22
12.85
3.14


MeO
B(pin)
CO2Et
CO2Et
2.26e
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 23 2016
168.227
167.748
158.383
150.399
132.404
113.61
82.966
61.443
61.101
58.240
55.143
43.896
40.503
14.054
13.750
220
200
180
160
140
120
100
80
60
40
20
0
ppm

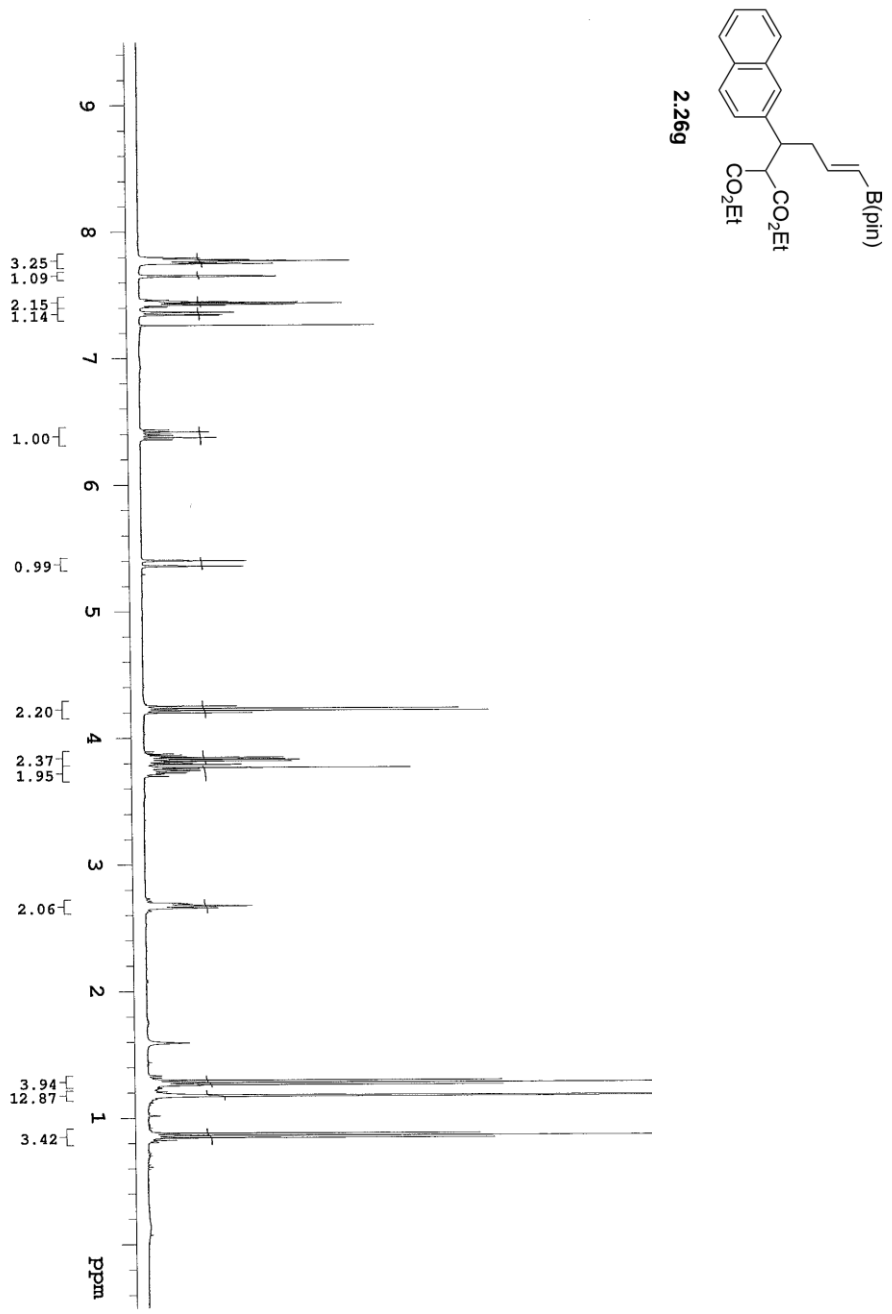

F3C
CO2Et
CO2Et
B(pin)
2.26f
2.18
2.23
1.00
1.00
2.26
2.26
2.19
2.15
4.38
13.22
3.31
ppm

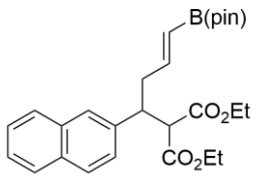


2.26f

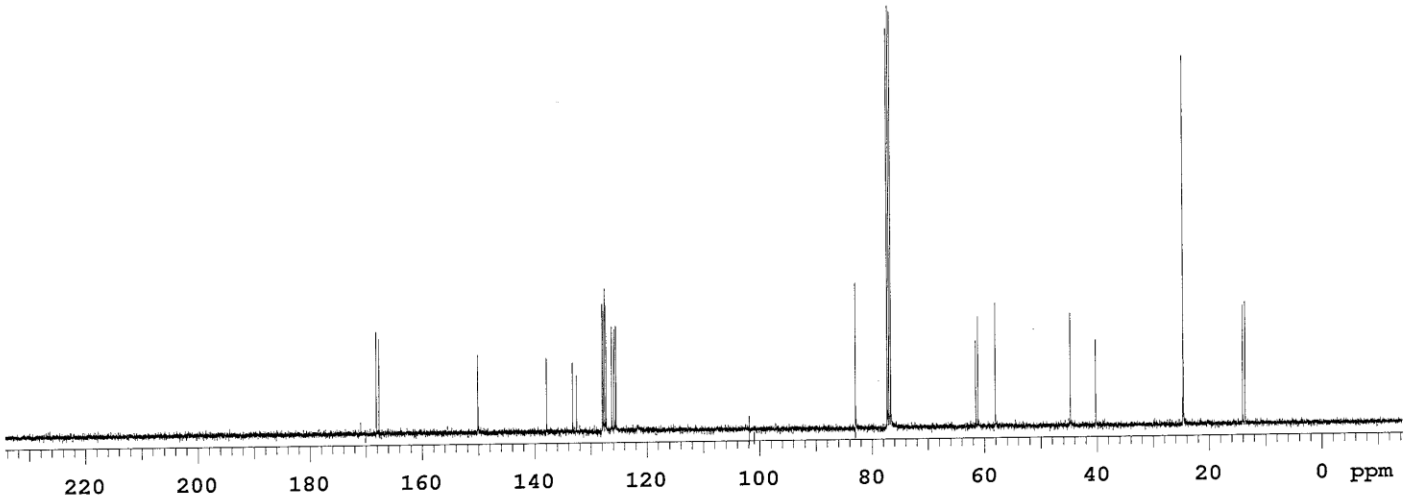
Zy-2-289-2p-13C

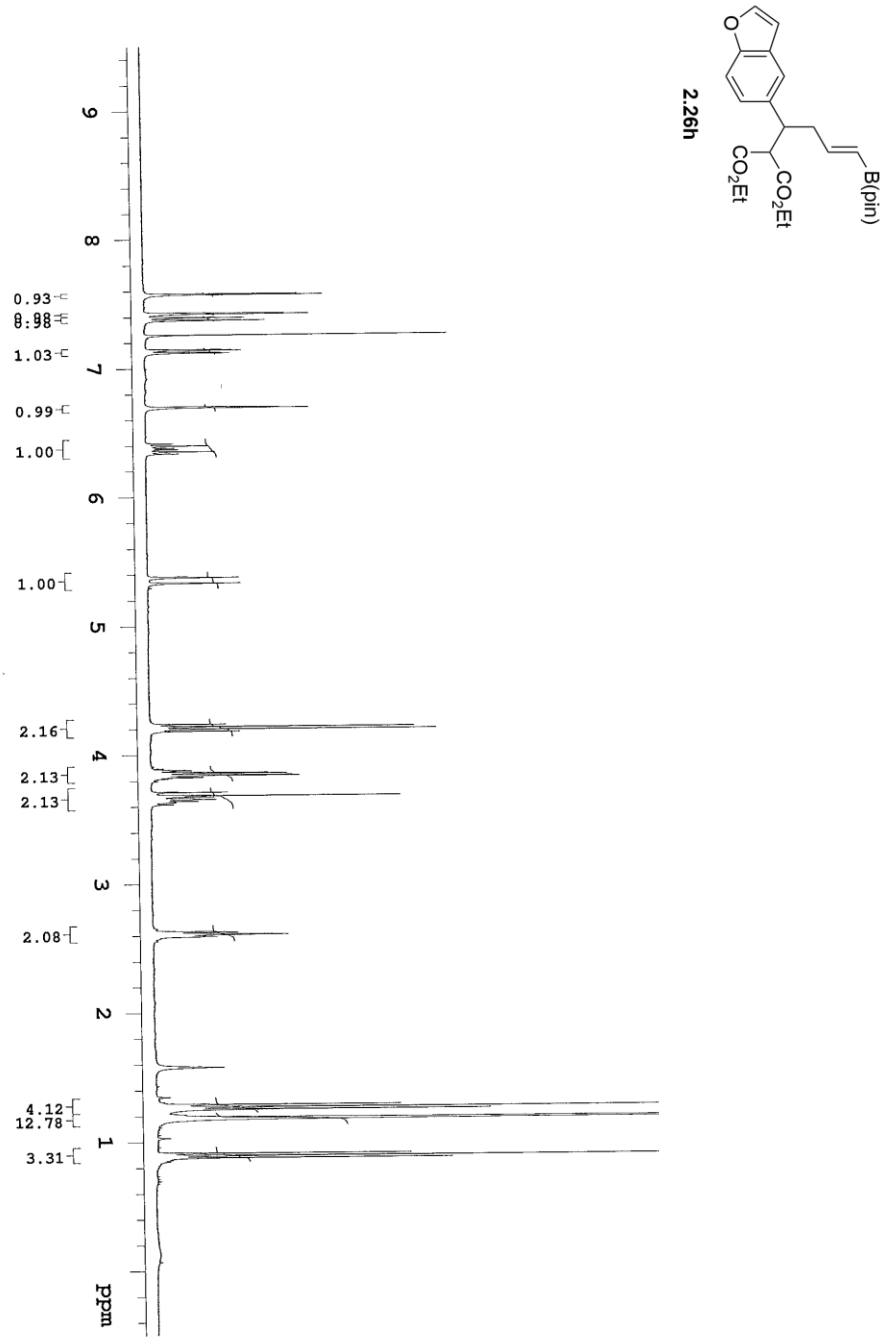
Sample Name	**Zy-2-289-2p-13C**	Pulse sequence	**CARBON**	Temperature	**25**	Study owner	**mengf**
Date collected	**2016-10-16**	Solvent	**cdcl3**	Spectrometer	**nmr13-vnmrs400**	Operator	**mengf**

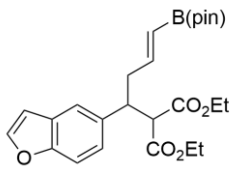

2.26g
B(pin)
CO2Et
CO2Et
3.25
1.09
2.15
1.14
1.00
0.99
2.20
2.37
1.95
2.06
3.94
12.87
3.42
ppm



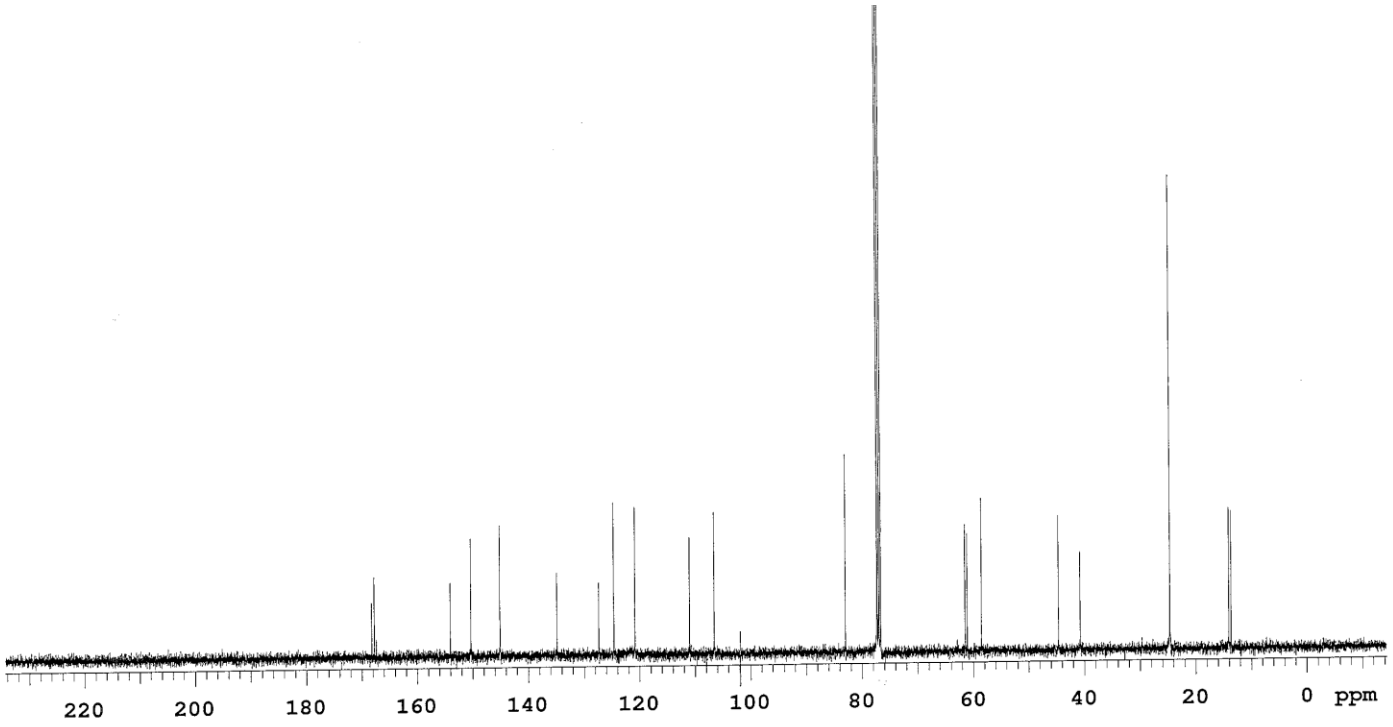
2.26g

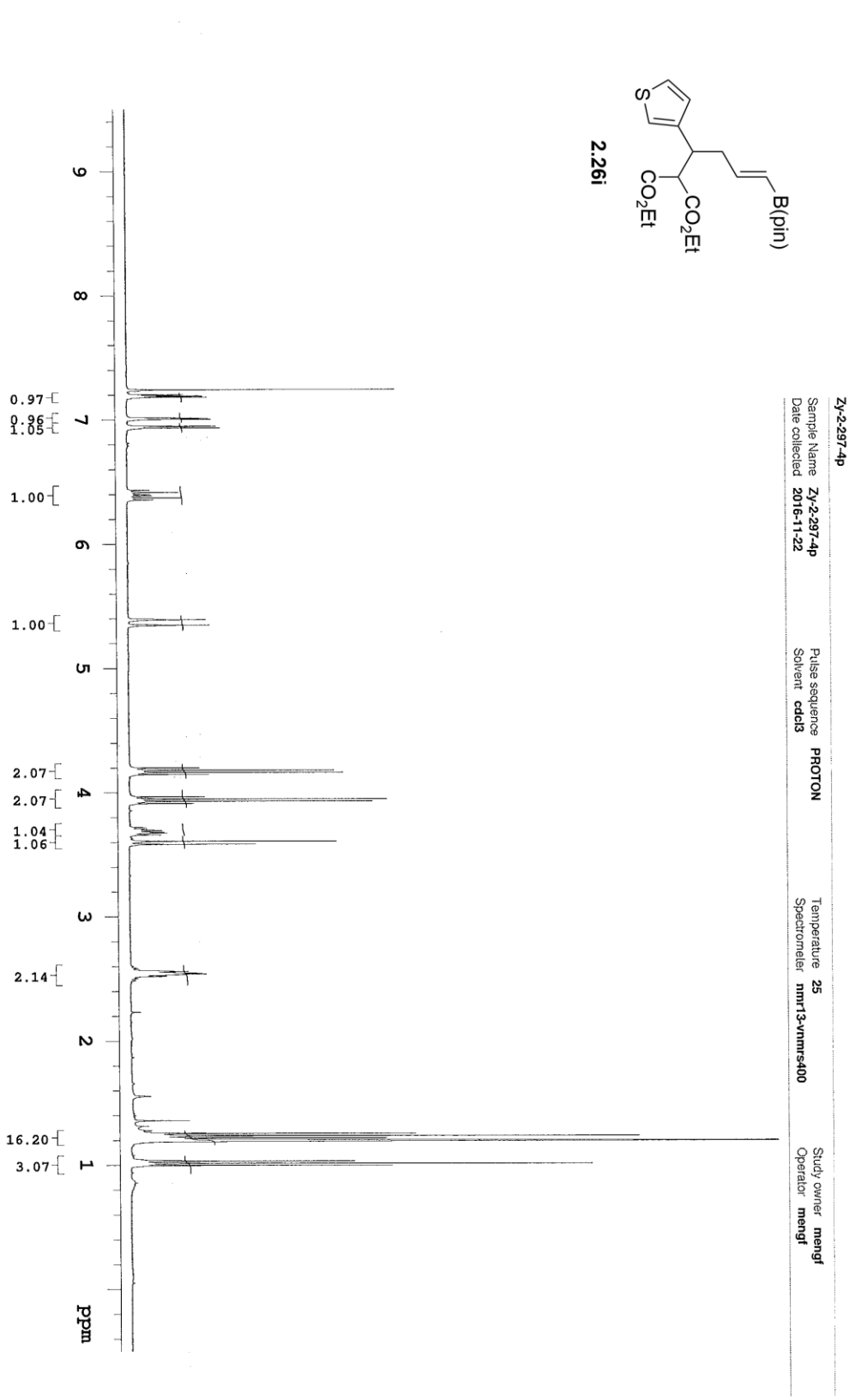


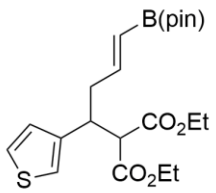

2.26h
O
CO2Et
CO2Et
B(pin)
0.93
0.98
1.03
0.99
1.00
1.00
2.16
2.13
2.13
2.08
4.12
12.78
3.31
ppm



2.26h




Zy-2-297-4p
Sample Name Zy-2-297-4p
Date collected 2016-11-22
Pulse sequence PROTON
Solvent cdcl3
Temperature 25
Spectrometer nmr13-vnmrs400
Study owner mengf
Operator mengf
B(pin)
CO2Et
CO2Et
S
2.26i
0.97
0.96
1.05
1.00
1.00
2.07
2.07
1.04
1.06
2.14
16.20
3.07
ppm



2.26i